DEPARTMENTS OF LABOR, HEALTH AND HUMAN SERVICES, AND EDUCATION, AND RELATED AGENCIES APPROPRIATIONS FOR FISCAL YEAR 2009

WEDNESDAY, JULY 16, 2008

U.S. SENATE,
SUBCOMMITTEE OF THE COMMITTEE ON APPROPRIATIONS,
Washington, DC.

The subcommittee met at 9:47 a.m., in room SD–138, Dirksen Senate Office Building, Hon. Tom Harkin (chairman) presiding.

Present: Senators Harkin, Murray, Durbin, Reed, Specter, and Cochran.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

STATEMENT OF HON. ELIAS A. ZERHOUNI, M.D., DIRECTOR, NATIONAL INSTITUTES OF HEALTH

ACCOMPANIED BY:

FRANCIS S. COLLINS, M.D., Ph.D., DIRECTOR, NATIONAL HUMAN GENOME RESEARCH INSTITUTE

ANTHONY S. FAUCI, M.D., DIRECTOR, NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES

ELIZABETH G. NABEL, M.D., DIRECTOR, NATIONAL HEART, LUNG AND BLOOD INSTITUTE

JOHN NIEDERHUBER, M.D., DIRECTOR, NATIONAL CANCER INSTITUTE

OPENING STATEMENT OF SENATOR TOM HARKIN

Senator HARKIN. Good morning. The Labor, Health and Human Services Appropriations Subcommittee will come to order.

Welcome to our hearing on the fiscal year 2009 budget for the National Institutes of Health. Last year you'll recall that this subcommittee held six hearings. I promise we'll do it in 2009, because I want to get back to that system of having all of the Directors back again, just—this year was just—a lot of things happening this year.

Senator COCHRAN. You think you're going to be chairman again?

Senator HARKIN. Well, let me put it this way—even if I'm not chairman, I'll bet the—the way we pass this gavel back and forth, it won't make any difference. He'd let me have them anyway, even if I wasn't chairman.

Anyway, we'll move on, here.

Before I begin, I do want to take a moment to thank Dr. Collins, for his extraordinary service as a Director of the National Human Genome Research Institute. Dr. Collins has been teaching me about genomics since 1993 when he first came to NIH, and I'd like to think that, at times during those 15 years, when I almost understood what he was talking about.

In fact, that's one of the things I admire the most about you, Dr. Collins. As brilliant as you are, you never talk down to your audience, you can converse as easily with the layman as with the Nobel Prize winner. In all the years that I've known you, I've never entered a conversation with you, without feeling smarter, and more hopeful about the future.

So, I think that that kind of a quality helps explain, again, why you were so successful in leading the Human Genome Project. An effort that, I believe, will go down in history as one of mankind's greatest achievements.

This has also served you well during your 13-year crusade to pass the Genetic Information Nondiscrimination Act, which finally became law in May. They call it GINA, for short, we think it should have been called "Francis", for short.

So, this will be Dr. Collins' final appearance before this subcommittee as the Director of the Genome Institute, but I strongly suspect that we'll see you here again in some other capacity, once you decide where and how you're going to apply your talents next.

Until then, Dr. Collins, on behalf of this subcommittee, and I think I can speak for every person on this subcommittee, thank you for all you've done, at NIH and throughout your career, to help improve people's lives. You will be greatly missed.

As for the matter at hand this morning, the NIH budget, we got some good news 2 weeks ago, when the President signed into law the supplemental that included $150 million for NIH. That's enough to award an additional 246 new research project grants, bringing the total for fiscal year 2008 to more than 10,000.

Even with that increase, however, fiscal year 2008 marks the fifth year in a row that NIH funding failed to keep up with the cost of inflation. In fact, since the end of the doubling period, in fiscal year 2003, NIH funding has dropped by about 10 percent in real terms. The average investigator now has a less than 1-in-5 chance of receiving an NIH grant. As Dr. Zerhouni has frequently lamented, the average age at which a researcher gets his or her first—RO1 grant, is now 42.

It should be no surprise, then, that many young people are deciding against a career in biomedical research, putting this Nation at risk of losing a generation of talented investigators.

Regrettably, the President responded by freezing NIH funding in his fiscal year 2009 budget. Under his plan, the success rate for research project grants would fall to 18 percent, the lowest level on record. But, rest assured, Congress will not accept this approach.

Last month, the Senate Appropriations Committee marked up the fiscal year 2009 bill. It includes an increase of $875 million over last year for NIH, on top of the $150 million in the recent supplemental.

Today, Senator Specter and I will introduce another supplemental appropriations bill that would add $5.2 billion for NIH.

This would be enough to restore the purchasing power of NIH that was lost to inflation since the end of the doubling period, plus provide $1.2 billion specifically for the National Cancer Institute, in line with the NCI's professional judgment bypass budget.

To elaborate, perhaps, on this or anything else, I now turn to my distinguished ranking member and great friend, Senator Arlen Specter.

OPENING STATEMENT OF SENATOR ARLEN SPECTER

Senator SPECTER. Well, thank you very much, Mr. Chairman, and thank you for convening this important hearing.

At the outset, Dr. Collins, I join the chairman in thanking you for extraordinary service. I thank all of you. I thank NIH, other medical professionals for the excellent care that I'm getting. As you can tell from my Telly Savalas look, I've had a recurrence of Hodgkin's. Had the last of 12 chemotherapy treatments on Monday. I'm constantly asked how I'm doing, and my slogan is tough, but tolerable. Good to have distractions so that I don't think about myself, and around here there are a lot of distractions.

Senator HARKIN. Why are you looking at me?

Senator SPECTER. Senator Harkin and I—well, if I look at Senator Harkin, it's an attraction, it's not a distraction. Not as decisive as an attraction as looking at Senator Bettilou Taylor but also an attraction.

Senator Harkin and I will be on the floor later today, as he's noted, with a supplemental appropriations bill for $5.2 billion. Regrettably, the prospects are that it's confederate money, and we have to do something about it, it's just a scandalous situation to have seen the NIH budget cut in recent years, with across-the-board cuts, which we can't control, at all, out of the subcommittee.

With the cost of living adjustments not maintained—again, which we can't control, because we've gone through the fat, the muscle and the bone, and there just isn't anything left in the subcommittee budget, when you have to compete with Headstart and worker safety and job training—the three departments which this subcommittee has. But we were determined, if I have a way, to do better.

As you know, we have asked for projections as to what it would cost to cure cancer. Now, I hear everybody talk about cure, which is in quotation marks, but really make a major assault—a major assault.

In 1970, President Nixon declared a war on cancer and had that war been pursued with the intensity of other wars, I wouldn't have gotten Hodgkin's and—we all have good friends who have died from breast cancer or prostate cancer, ovarian cancer—just rampant. We can do better. A lot better.

Of course, you can't just move for the National Cancer Institute, there has to be parity with other NIH funding.

We're taking a look at a collateral line, which may have some overlap on a funding stream, or may not. That is the issue of Advanced Directives. For some time now, Senator Harkin and I, in our subcommittee, have included in the request to Medicare to put in information on Advanced Directives. It hasn't worked out too

well, and obviously, nobody should tell anybody else what ought to be done on that situation.

I talked to the Secretary of Health and Human Services, Mike Leavitt, about it, and projecting the savings that might be obtained from advanced directives, the thought is there might be an incentive with a discount on Part B payments. One of my colleagues, Senator Johnny Isakson, has an idea to make an advanced directive mandatory before coming into Medicare—maybe that's too strong, but which way you go, it doesn't matter, if you take an Advanced Directive for life support, or not.

We're trying to get a projection as to what we're doing—we just had a bloody political battle on Medicare, as you all know. Regrettably, we got it behind us, not with a lot of blood on the ground on the Senate chamber and from here to the White House, with condemnatory statements coming from the President yesterday about nine people who shifted their votes.

I was asked about it, and what did I think about the President's veto, and the President's statement. I said, "Well, I respect the statement, I hope he would respect the Senators." We all have our constitutional role to play.

But these are big, big issues which this committee is in the center of, and we've got the greatest experts around.

As I told the chairman a few moments ago, I'm blanking on Judiciary, and there was a hearing that's going to start in 2 minutes, and I have to be there for the opening part of it, but I will return very, very shortly for this important hearing.

Thank you, Mr. Chairman.

Senator HARKIN. Thank you.

Senator Durbin.

STATEMENT OF SENATOR RICHARD J. DURBIN

Senator DURBIN. I'm anxious to hear the testimony, but I wanted to be here today, first to thank Senator Harkin and Senator Specter—it really is hard to imagine that any of us could go home to our States and explain to the people of this country that we can not afford medical research.

Yet, the fact is that after a dramatic increase in NIH funding, during the period when a Congressman from my State, John Porter, was chair of the appropriate House subcommittee, we have seen this whole area of medical research fall under this administration—not keeping up with medical inflation—let alone, inflation—in most instances. I think that that is shameful. I don't believe it's defensible, morally or politically.

I want to thank Senator Specter and Senator Harkin for continuing their battle to fund this important agency.

The major reason I'm here, and the questions I'll go to comes down to something that virtually every Senator faces, almost every day. When somebody comes in our office and says, "My son is dying, why aren't you spending more in research to find a cure for his disease? Why is the NIH spending so little for the research to spare him, and so many others who can die?"

We sit here—I sit here—wondering—is that person right? Are we doing the right thing for medical research? Are we putting the money in the right places? I don't know the answer to that ques-

tion, having been around Capitol Hill for a long time. I'm going to ask them that later.

Thank you, Mr. Chairman.

Senator HARKIN. Senator Reed.

STATEMENT OF SENATOR JACK REED

Senator REED. Mr. Chairman, I too am here to thank and commend you and Senator Specter for your extraordinary leadership over many years. You've never let go of this issue, and you're responsible, collectively, for some of the vast improvements in NIH over many years.

Let me also echo the concerns that Senator Durbin expressed, and one other, which is that it's not just about the relatively new therapeutic techniques. It's also maintaining a new generation of researchers and scientists. As this funding decreases we're seeing more and more of these very talented, young academic researchers go elsewhere.

I had a chance to visit a Brown University researcher, Dr. Teresa Serio. She related to me that she was one of 30 Ph.D. students at Yale University—she's the only one now still in academic research, because the grants weren't there to support the applications to go forward, to get tenure, to do all the things you have to do. So, this is about the infrastructure of our research endeavor, and how it's also critical.

Thank you.

Senator HARKIN. Thank you very much, Senator Reed.

Senator REED. I have a statement for the record, too, Mr. Chairman.

Senator HARKIN. Okay, it will be made part of the record.

[The statement follows:]

PREPARED STATEMENT OF SENATOR JACK REED

Research to prevent debilitating diseases has the potential both to ease patient suffering and lessen the burden on our health care system. For this reason, I was proud to support the historic doubling of funding for the NIH from 1998 to 2003. Unfortunately, since then our Nation's commitment to this critical research has wavered.

Recently, a group of concerned universities and research institutions—including Brown University in my State—released a report that documents how flat funding for the NIH puts a generation of science at risk. Since 2003, the purchasing power of the NIH has eroded by 13 percent. As a result, only 24 percent of research projects are funded, and the average age of first-time grant recipients is 43. The report finds that there is a real risk that we will lose aspiring scientists to other industries or overseas.

Of course, flat funding puts at risk not only the development of scientists, but also their science—cures and treatments for chronic diseases that exact a costly human and economic toll. Rhode Island ranks 44th in the prevalence of chronic diseases such as cancer, diabetes, and heart disease. In 2003, the cost of treating these conditions was $1.2 billion and the economic cost in lost work and productivity was $4.5 billion. Obviously, an investment in research on these conditions would improve both the health of Rhode Islanders and the health of the Rhode Island economy.

To show the real-life impact of stagnant funding, I want to tell you about Dr. Tricia Serio, a researcher at Brown University. Dr. Serio is ready to research ways to reverse the spread of proteins that damage the brain in several devastating diseases, including Alzheimer's, Huntington's, and Parkinson's. For years, the NIH said that her ideas were very innovative, but too risky. The NIH did not award her a grant until 4 years after she joined Brown.

Dr. Serio has directly observed the effect of flat funding on her generation of scientists. She says that when she was at Yale, there were 30 Ph.D.s in her program;

but she believes that she is the only one who is still pursuing a career in academic science.

The NIH should not be forced to make the difficult decision to turn down research that is innovative, but risky. We did not send a man to the moon by being overly cautious. Nor will we discover a cure for cancer unless we make a significant investment.

Mr. Chairman and Ranking Member, I am pleased that your bill increases funding by 3.5 percent to keep pace with biomedical inflation for the first time in 6 years. This is an increase of over $1 billion over last year and the President's request, which was extraordinarily shortsighted.

I hope that we will pass this bill soon and that the President will reconsider his priorities. He should consider the stories of researchers like Dr. Serio, who are on the cusp of scientific breakthroughs, but desperately need our support.

Thank you.

Senator HARKIN. Senator Murray.

I would just submit my statement for the record, I apologize for being a few minutes late. I really look forward to the testimony and opportunity to hear from all of you. I agree with everything I've heard this morning, that the investment's critical, the research is critical and just, to all of you, a lot of Americans, and people around the world's hope lands right in your lap as they are hoping that something that you discover or something that one of the scientists does changes their lives.

So, we really appreciate the tremendous work you do, and are very proud of the support of this community, Mr. Chairman, I want to thank you personally for your attention to this.

[The statement follows:]

PREPARED STATEMENT OF SENATOR PATTY MURRAY

Thank you, Senator Harkin and Senator Specter, for holding this hearing.

I appreciate your long-time support for the National Institutes of Health. And I'm proud of this committee's leadership supporting research and other important health care issues.

For more than a century, NIH has played a vital role in improving the health of our Nation.

By conducting and supporting research on everything from breast cancer to autism, NIH is helping to improve our understanding of what causes diseases—so we can predict when they will occur and develop the tools to better fight them.

Its work gives tremendous hope to the many Americans who suffer from a number of devastating diseases. And I believe that every dollar invested can save money later in reduced health care costs and economic productivity.

That is why I have been extremely discouraged by President Bush's proposed funding levels for NIH.

If President Bush's budget becomes reality, fiscal year 2009 will be the sixth year in a row that funding for the NIH was frozen at $29.3 billion.

That fails to keep up with biomedical inflation, and it would cause the projected success rate for research grant applications to fall to the lowest level since 1970.

Fortunately, this year, we are taking steps to turn the tide.

The Senate's Labor-HHS Appropriations bill increases NIH's budget by 3.5 percent, enough to keep up with inflation.

While I wish we could do more, this is a step in the right direction.

It has been almost 6 years since we increased NIH funding. In fiscal year 2003, when we doubled the budget, we enabled NIH to advance into new areas of science and to support far more promising research than ever before.

Our continued investment will ensure that there are enough trained professionals ready to turn today's research advances into tomorrow's treatments, diagnostics, vaccines, and cures.

And I look forward to working with my colleagues to continue support its progress.

Senator HARKIN. Thank you very much, Senator Murray.

Again, Dr. Zerhouni, thank you very much, and thank all of you for being here today. Like I said, just because of schedules, this

year I was unable to do what we did last year, and so I thought it was at least important to have you here to go over the budget and to respond to some of our inquiries, perhaps on what's happening at NIH, with the panel that you have in front of you, which represents the—perhaps the largest of the institutes at NIH.

So, Dr. Zerhouni, again, welcome. Thank you for your great leadership, and please proceed as you so desire.

SUMMARY STATEMENT OF HON. ELIAS A. ZERHOUNI

Dr. ZERHOUNI. Thank you, Mr. Chairman, and members of the subcommittee. My colleagues and I are really pleased to be here, and we have submitted written testimony for the record, but what I'd like to do in my oral presentation is to really give you perspective about what has been the return investment which was testified to, over the years at NIH, in terms of benefits to the public.

But today, what I'd like to stress is, in parallel to the difficulties we have to sustain momentum, there is an incredible opportunity that is facing us, that has come from the work of my colleagues, in particular, from the completion of the human genome.

I would like to spend a few minutes with you, to describe for you what is it that NIH faces in terms of scientific challenge—you have the core issues that, from the scientific standpoint we see, that members of the subcommittee should focus on, and help us address.

So, what I'd like to do, first and foremost is give you, if you'll allow me, a little lesson on the complexity of biology and where we're going.

First and foremost, over the past 10 years, we have discovered methods, ways, approaches, ideas, technologies, and methodologies, that tell us that we can do four things we couldn't do before.

One, we can be a lot more predictive about exactly how a disease develops, in whom it develops, and what are the markers that tell us that someone is susceptible to a disease process—that's predictive.

The second, we can be much more personalized about how we treat an individual, because we do realize today that none of us are exactly made like anyone else—we're individuals, and individual variability means that we have to tailor therapies to the individual.

The third, for the first time in history, we can foresee an era where we can be preemptive, where we can act years before the disease strikes a patient, and basically keep the patient healthy, rather than wait for the disease to affect the patient, and for the doctor to intervene.

So, we're moving from what we call a late intervention, reactive paradigm, to an early intervention, proactive paradigm, which will require the fourth P, which is participation.

Now, participation is essential—Senator Specter is a fire—he really participates in his own care, and this is key to the success he's had in battling cancer.

We see this as the future of medicine. Without understanding that, and I understand the future paradigm is very difficult to understand, but the strategies at NIH have been to advance our knowledge and to benefit the American public. See Figure 1.

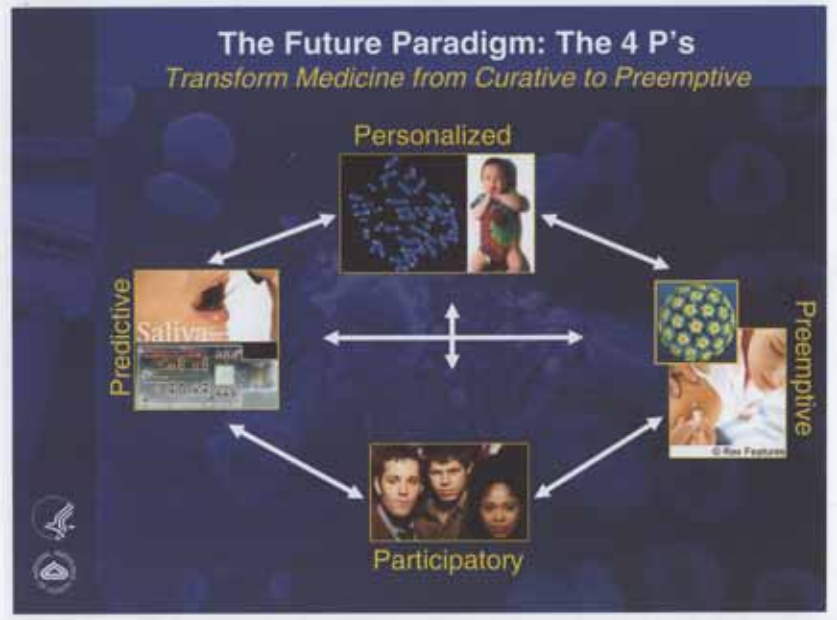


FIGURE 1.

So, let me just go forward here, and tell you the concept that is essentially emerging in front of us, and that is, the concept of complexity of disease processes.

It is our understanding today that there's no disease that can—that comes from any one particular molecule in the body being diseased. In fact, most of us are a combination of a network of molecules, as described on the side, that interact constantly.

NORMAL GENE FUNCTION—HEALTHY STATE

For example, here I have described five proteins—A, B, C, D, and E—all of these proteins are related to each other in the complex network. Over the past 50 years, since the discovery of the structure of DNA, what we have done is to try to understand how these proteins are interacting with each other. See Figure 2.

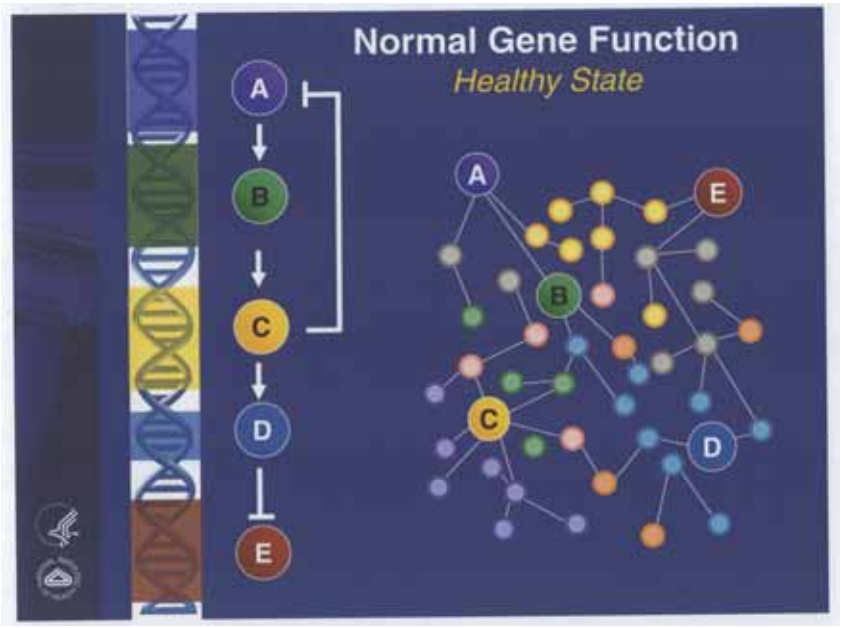


FIGURE 2.

As we discover the genetic code, and we discover that, in fact, every protein in our body is really made through—by instructions that are embedded in our genetic code through a process of transcription and translation—then they understand that fundamentally to understand the healthy state, and the disease state, we need to understand the components.

So, for example, in this case, A, B, C, D, and E are proteins that are encoded by DNA. So that, if you look at each one of them, you know that they are made upon instructions by DNA, and each one of them is made in a certain amount, a certain shape, and each one of them interacts with the other.

DISRUPTED GENE FUNCTION—DISEASE STATE

So, what happens when a disease process occurs? One of the theories that we have worked on, over the past 25 years is that, perhaps, instead of having a concept of disease that is related to one protein creating one disease, perhaps what is more important is to understand how they all interact.

But when we observe a disease process, we need to know which part of the code is abnormal? Where we do that, where we find, for example, what we have discovered over the past 5 years, in great part due to the work of Dr. Francis Collins, is that when there is a bad instruction in our genetic code. For example, as I showed here with that little mark, what happens? Well, that instruction translates itself into a protein that, instead of being shaped normally, as a round circle, is now abnormal.

So, what happens downstream in all of these molecules that keep us healthy, one of them will be abnormal, as you will see, that molecule now is completely misshapen. But that C molecule does not act by itself—it acts by interacting with A, and by repressing, for example, the amount of A, so the amount of A will increase. So on, we can see decreases in others. This is the disease state. See Figure 3.

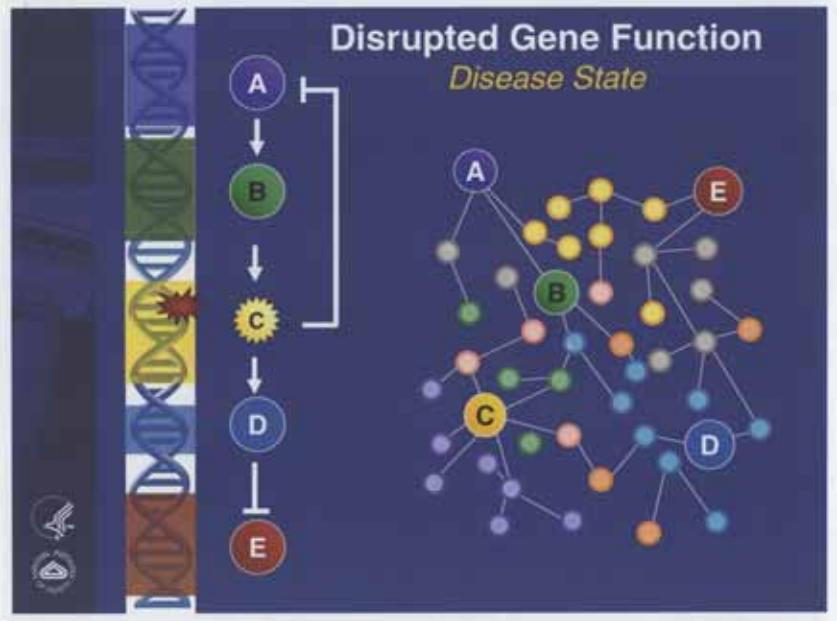


FIGURE 3.

So, the question we have faced over the past 15 years is, how can we discover all these code abnormalities, the things that we carry with us, that make us susceptible to disease, and how do we understand the environment interacting with it, in the context of a much more complex biology than we even thought in 1971. In 1971, we thought we would find silver bullets for cancer. Now we know that cancer is not one disease, not one pathway, not one interaction, but many. We need to understand them to be able to cure them.

GENOME-WIDE ASSOCIATION DISCOVERIES

So, let me tell you, then, what happened in my tenure here as Director of the NIH since 2002—and in a slide provided to me by Dr. Francis Collins in 2005—how much we knew about these abnormalities in the genetic code that may have an impact on a particular molecule, or a disease process. See Figure 4. This is, basically, the discovery panel that I have in my office, trying to get the reports from everyone about what I was discovering in disease processes, according to that template that I showed you. That template is essential to comprehend, and it is essential to understand that, this is where the battle is, today, and this is where the re-

sources need to be put in, and we do not have the resources to pursue all of these hints, if you will.

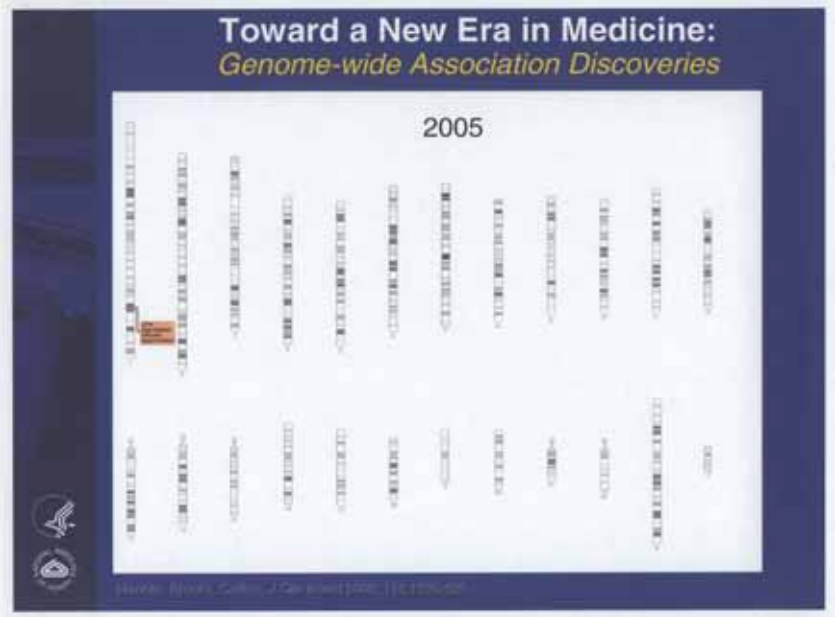


FIGURE 4.

In 2005, what you see here are all of the chromosomes of the human body—all of these marks here are chromosomes. All of these chromosomes, essentially, are the genetic code. So, when you make a discovery, somebody puts a little flag on the chromosome and says, "Gee, we made a discovery, here." Patients who have this disease, had this abnormality right there.

In 2005, we found that in age-related macular degeneration, which is a major cause of blindness in our seniors, for years we thought it was a degenerative disease. Then, all of a sudden, someone discovered that the gene that was abnormal was an inflammatory gene, that led to the inflammation.

So, all of a sudden, now, we have new treatments, because we have a completely new understanding of that complex network that I described.

Look at what happens in 2005, and this is 2006: three more discoveries. See Figure 5. I was really elated, I thought this was great. Finally, we're breaking the code, we're going to be able to find some leads—then look what happens. First quarter of 2007, I had more discoveries reported to me than in the entire years of 2005 and 2006—that's the first quarter of 2007. See Figure 6. Second quarter of 2007, I had even more discoveries than all of the cumulative discoveries that were made in my 5 years as NIH Director, just in the second quarter of 2007. See Figure 7.

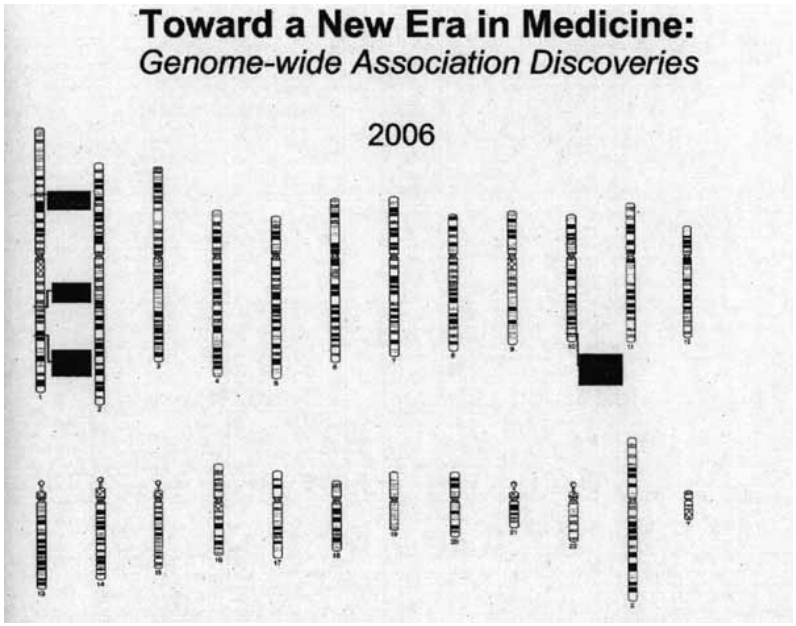


FIGURE 5.

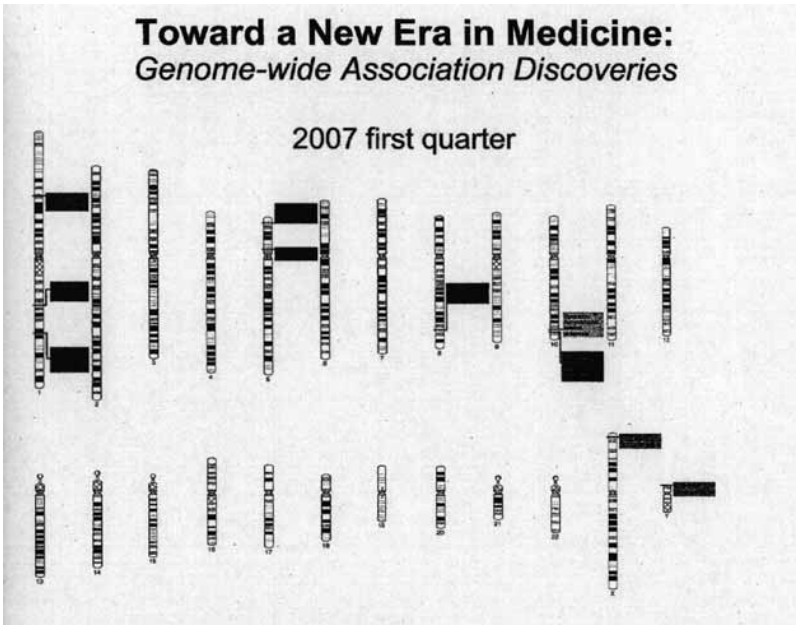


FIGURE 6.

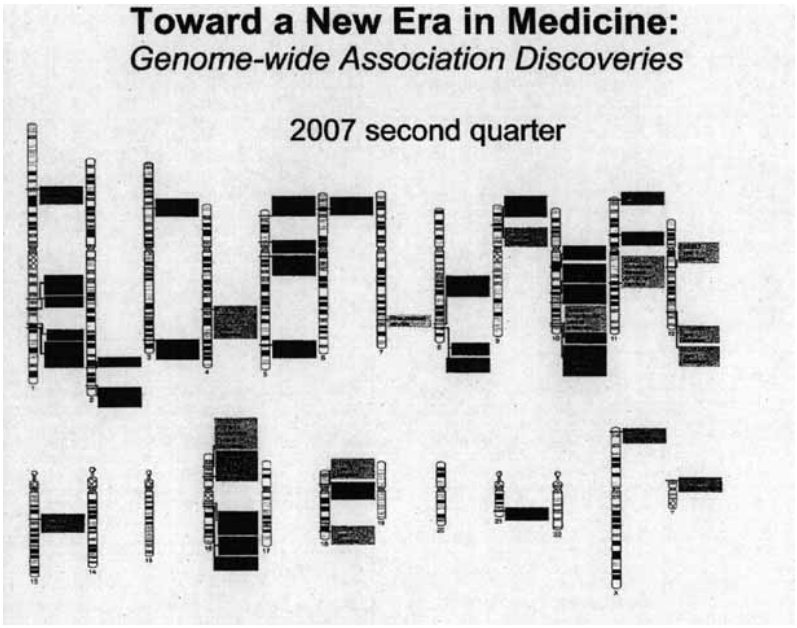


FIGURE 7.

In the third quarter of 2007, fourth quarter 2007, first quarter of 2008, and the second quarter of 2008. See Figures 8, 9, 10, and 11. This is nothing short of an explosion of knowledge. This is not something that we can drop, this is not something that we can just leave on the floor and say, "Our job is done." These are clues that tell us about dozens of diseases.

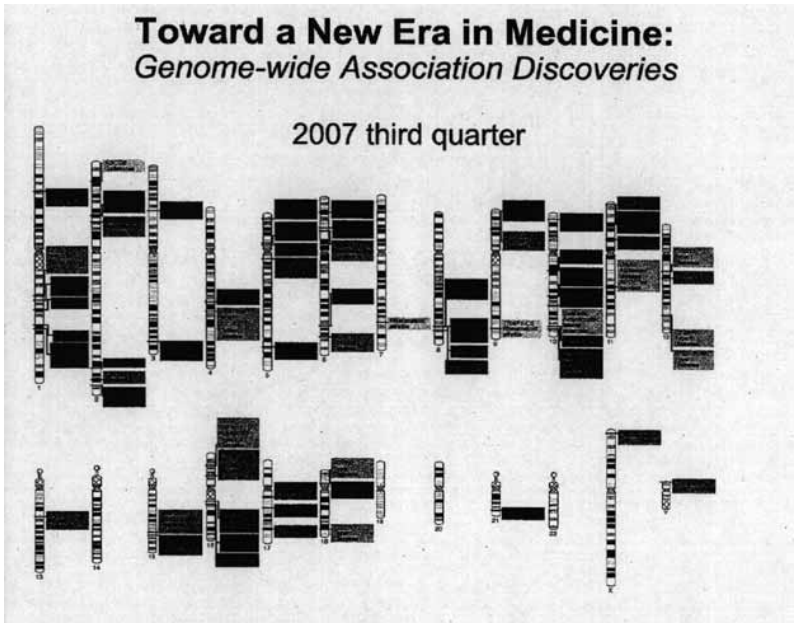


FIGURE 8.

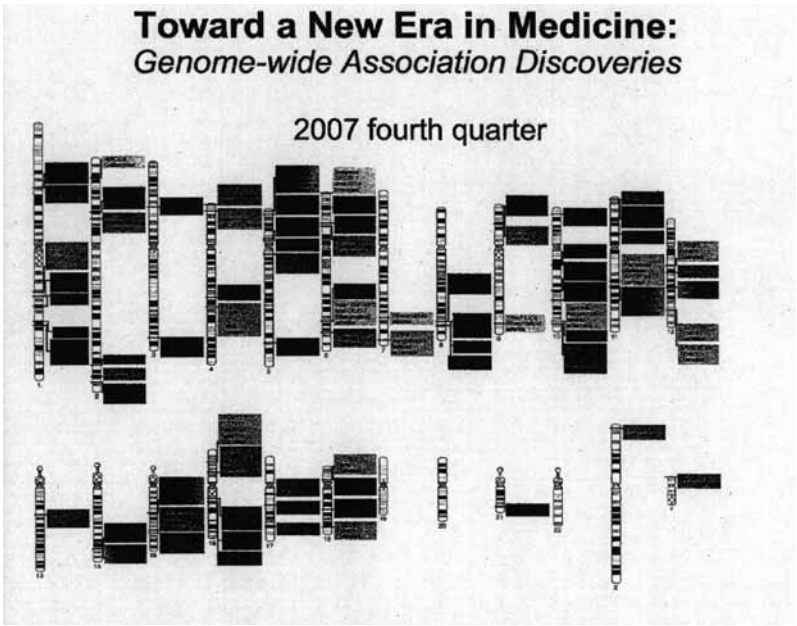


FIGURE 9.

FIGURE 10.

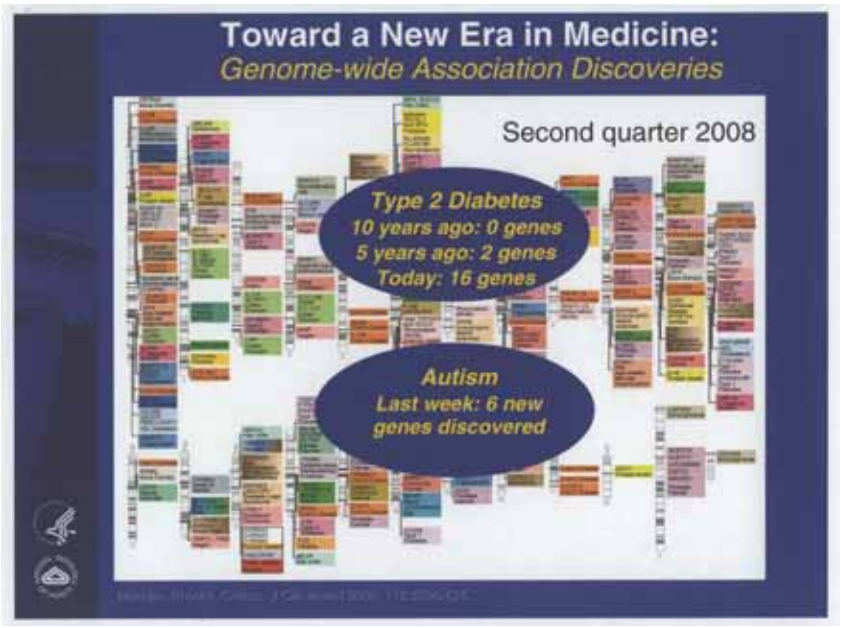


FIGURE 11.

For example, Type II diabetes—10 years ago, we knew about nothing, we knew zero genes that were important in diabetes. Many people had worked on it, couldn't find them. Five years ago, we have two genes, today 16 genes. I'm told in the next few days or weeks, a new paper is going to come up, identifying 14 essential genes that underlie that network that I described, that is abnormal in diabetes.

If you look at autism, last week—only last week, we received a report, a landmark report—identifying six new genes, and telling us something about this disease we didn't even know 3 years ago. So, the explosion is enormous, but does that mean our work is done?

Actually, let me show you what we, as scientists, believe are great opportunities. I showed you genetic abnormalities in what we call our inherited genome, things that we're born with. But cancer is a different process. The genome of cancer can become abnormal during our lifetime.

OPPORTUNITIES IN CANCER RESEARCH: NEW GENOMIC CLUES

So, the National Cancer Institute and the National Human Genome Research Institute engaged in a program, a pilot project called the Cancer Genome Atlas, and guess what? Two weeks ago, they reported the first finding in one of the most deadly cancers, brain cancer, glioblastoma, and we reported three new genes, we had absolutely no idea that they were critical to the development of glioblastoma. See Figure 12.

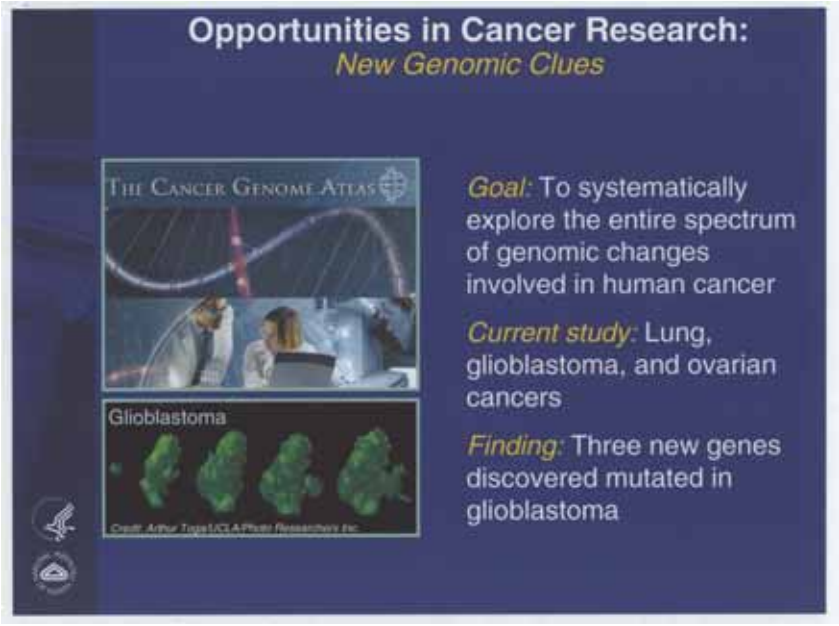


FIGURE 12.

This is happening in front of our eyes. Members of the subcommittee, I cannot tell you that the feeling I have is that we're witnessing, right in front of us, a revolution in knowledge. The question is, are we going to be able to take advantage of it? To take advantage of it is a rigorous process, that requires NIH to be extremely proactive, dynamic, flexible, and adaptive. But how?

THE NEXT STEPS IN UNRAVELING THE MYSTERY

Let me just show you with this slide what the process is. See Figure 13. Once you have a clue, like the many clues that I described, the first thing that you have to do is invest immediately in analyzing more populations and more genes, so that that clue becomes a real lead, so that you confirm it—not just one lab reporting a finding, you need two, three labs reporting that finding, so we can follow that lead. Just like a detective, you go after that lead. That's step one.

FIGURE 13.

Once you have that lead, you need to understand, where does it fit in that complex network that I described—how does the biology work? Once you have understood the biology, now we have a real target to go after. So, you go from clue to lead to target, and then you have to make the investment to translate that into either diagnostics, a prevention strategy, or a therapeutic strategy, and we have done that in many diseases—now we have a way to do it systematically in almost every common disease that we know.

So, this is really the challenge, are we going to drop these clues? Drop these leads? Are we going to have the new next generation of scientists that are going to dedicate their lives in exploring what

has come up through the 10 years of very hard work that all of us at NIH have done?

The game is to transform medicine. We cannot practice medicine in 20 years the way we do today. It will have to change, otherwise, we will not sustain, the cost of healthcare that is facing us. It can only be done through renewed discovery, through renewed investments and trust that, in fact, only knowledge, only discovery will provide the solutions.

PREPARED STATEMENTS

So, with that, I'd like to thank you, and again, repeat my admiration for Chairman Harkin, and ranking member Specter, and all members of the subcommittee, you've shown a deep understanding of the challenges in front of us, and we appreciate it very much.

We're ready to answer your questions.

[The statements follow:]

PREPARED STATEMENT OF DR. ELIAS A. ZERHOUNI

Good afternoon, Mr. Chairman, and distinguished members of the subcommittee. It is a privilege for me to appear before you today to present the National Institutes of Health (NIH) budget request and to discuss the priorities of NIH for fiscal year 2009 and beyond.

Before I begin, please allow me this opportunity to express my appreciation to you and your staffs for your continued support of the National Institutes of Health.

As you are aware, research is the basis of virtually every improvement in health and medicine. The impact of scientific research, however, extends far beyond disease. Throughout history, advances in science and technology strengthened our economy, raised our standard of living, enhanced our global leadership, and lengthened and improved our lives.

To sustain these achievements, the flow of new scientific knowledge must be both continuous and substantive. Despite monumental progress, science remains a difficult frontier to explore. In this century, our society faces even greater challenges to the human condition that will require innovative and unprecedented scientific and technological advances across all fields of science, but most particularly in the life sciences. NIH's investment of $29.5 billion in fiscal year 2009 will be used to support such advances.

NIH plays a significant role in the extension of life, and the prevention and treatment of many diseases, transforming modern research, and medicine in countless ways. For example, not long ago, acute, short-term, and lethal conditions such as heart attacks, stroke, acute infections, and cancers were the dominant causes of early mortality. Today, life expectancy has markedly increased due to progress made in reducing death from such acute conditions. However, these advances indirectly led to a major rise in the burden of chronic long-term conditions. It is estimated 75 percent of today's healthcare expenditures relate to chronic diseases. The emergence and consequences of chronic conditions—like obesity, diabetes, or Alzheimer's disease—are examples of the challenges we face. Healthcare costs are rising exponentially. We must continue our focus on not only how we best deliver healthcare, but more importantly, what healthcare we deliver.

A NEW STRATEGIC VISION FOR MEDICINE

Given this dramatic shift from acute to chronic disease, the strategies for preventing and treating diseases are beginning to shift. Today, we intervene late when the patient exhibits symptoms of disease. Our research is changing this approach, so that we may intervene much earlier in the natural cycle of diseases, years before they strike their victims. We must now develop a much more pre-emptive approach that manages disease over its entire life cycle, from identifying an individual's susceptibility to a disease, to prevention, early diagnosis, reduction of complications, and smarter therapies.

This shift from a late curative paradigm to an early pre-emptive one is becoming increasingly possible, thanks to the avalanche of recent discoveries funded by NIH. For example, in 2002, when I became NIH Director, we knew of one important gene abnormality in type 2 diabetes. In the last year alone, researchers uncovered seven

new genes or genetic regions that provide new clues to how this disease may develop. Remarkably, I now receive about one report a week of a significant discovery in the field of genomics. Recent discoveries apply to a broad spectrum of chronic diseases, ranging from mental disorders to autism. We now can see a clear path to what we call "the 4 P's of Medicine": medicine that will be more Predictive, Personalized, Pre-emptive, and Participatory.

To reach these key long-term goals, NIH is strategically investing in research to further our understanding of the fundamental causes of diseases at their earliest molecular stages. However, individuals respond differently to environmental conditions, according to their genetic endowment and their own behavior. In the future, research will allow us to predict how, when, and in whom a disease will develop. We can envision a time when we will be able to precisely target treatment on a personalized basis to those who need it, thereby avoiding treatment to those who do not. Ultimately, this individualized approach will allow us to pre-empt disease before it occurs, utilizing the participation of individuals, communities, and healthcare providers in a proactive fashion, as early as possible, and throughout the natural cycle of a disease process.

This prospective management approach to disease is vital to the transformation of medicine of tomorrow. Today's discoveries are paving the way to make this future a reality. NIH continues its research efforts to search for cures to alleviate the suffering of the millions already affected by disease—and is greatly expanding the scope of research to discover entirely novel ways to stop disease in its tracks before it cripples us. This entails investing in completely new areas of investigation, while sustaining the level of our current efforts and supporting talented scientists using novel methodologies to explore new ideas and concepts that were impossible to envision only a few years ago.

TODAY'S SCIENTIFIC ADVANCES ARE TOMORROW'S MEDICINE

Consider how more predictive and personalized treatments could improve the safety and effectiveness of medications. The same medication can help one patient and be ineffective, or toxic to another. With the emergence of a field of research called pharmacogenomics, we will increasingly know which patients will likely benefit from treatment and which will not benefit, or worse, be harmed. Good examples of the present usefulness of pharmacogenetics are for cancer chemotherapy and use of the anticoagulant Coumadin.

Research on viruses is improving the lives of Americans and people around the world. NIH supported the early research that led to the discovery and development of antiretroviral therapies for HIV/AIDS. Today, antiretroviral therapies are benefiting millions of Americans as the most effective means of treating HIV infections. These therapies are also helping millions of people in Africa and the Caribbean through the President's Emergency Plan for AIDS Relief.

Current HIV/AIDS therapies focus on the virus itself. Researchers are trying to understand how the virus enters the human cell and hijacks the cellular machinery, so it can replicate and spread. In a recent experiment, researchers made significant progress toward reaching this goal. Their new approach is based on a process called RNA interference discovered in 1998 and recognized with a Nobel Prize in 2006. Using RNA interference, the researchers suppressed the activity of every single gene in a type of human cell. They discovered more than 276 human proteins that seem essential to the replication of the HIV virus in human cells. This experiment, unthinkable a few years ago, can now be exploited to develop new ways of disabling this deadly virus.

Fundamental research can unexpectedly lead to revolutionary breakthroughs. Scientists at the National Cancer Institute, for example, developed a virus-like particle technology that formed the basis for new commercial vaccines that target specific cancers. In June 2006, the U.S. Food and Drug Administration approved the vaccine Gardasil, which is highly effective in preventing infections from the four types of human papilloma virus (HPV) that cause the majority of cervical cancers in women. Worldwide use of this vaccine could save the lives of 200,000 women each year. This is the first example of a truly pre-emptive strategy in cancer.

More often than not, it is the sustained combination of multiple approaches—from the most basic science to epidemiological and behavioral research—that makes advances in science effective. One important public health success story is the reduction in tobacco use and related diseases. In the last decade, overall cancer death rates dropped for the first time in a century, driven largely by the dramatic reduction in male smoking from 47 percent in the 1960s to less than 23 percent today. This reduction, along with more effective early screening tools like mammography and colonoscopy, is changing the landscape of cancer mortality. These successes re-

flect the outcome of significant research investments made by many NIH Institutes and Centers (ICs) and our sister agencies over the last 50 years.

Our ability to predict and pre-empt disease also hinges on the development of new diagnostics based on recent discoveries in genomics, proteomics, systems biology, and imaging. Among the diagnostic capabilities currently being explored are:

Point of Care Diagnostic Testing.—NIH supports research that has and will develop technologies that offer instant diagnosis in the emergency room or physician's office, or at home, including rapid analysis of blood for assays such as chemistry, electrolytes and blood gases; biosensors that instantly detect signs of heart disease or infections; and biochips that detect disease processes at the molecular level.

Salivary Diagnostics.—Scientists identified genes and proteins expressed in salivary glands that we believe will replace some forms of urine or blood analysis in the detection of cancer, heart disease, diabetes, and other conditions.

Optical Imaging.—NIH-supported researchers are developing imaging techniques that seek to reduce the need for invasive diagnostic procedures. These new tools include fiber optic probes to detect malignant tissues, with the potential of avoiding invasive biopsies with a more accurate method of analysis; optical coherence tomography to identify heart disease; and multiphoton microscopy to study living cells and tissues.

Brain-Wiring Diagrams.—NIH-supported researchers developed a way to reveal connections made by a single nerve cell in living tissue. We hope one day to construct a wiring diagram of the billions of nerve cells that constitute the brain's visual centers that might allow us to diagnose and treat vision loss with far more success—an advance that has implications for many other brain diseases as well.

Autism Genes.—Research into autism discovered clues that rare genetic changes represent a risk for autism. With this preliminary result, we are on at least one path to understanding methods of predicting autism risk in infants.

THE CHALLENGES THAT LIE AHEAD

We are optimistic about recent discoveries. However, there are challenges that lay ahead of us. We still need to focus much of our efforts on fundamental research, because new threats and diseases constantly emerge. For example, soldiers suffering from blast injuries highlight the importance of additional knowledge on traumatic brain injuries. Infectious diseases remain among the leading causes of death worldwide. More than 30 newly recognized infectious diseases and syndromes emerged in the last three decades alone, including HIV/AIDS and SARS. Infectious diseases that once seemed to be fading, such as tuberculosis and malaria, have resurged. New drug-resistant forms of once-easily treated microbial infections are emerging at a rapid pace. New strains of influenza occur each year. There is concern that a new influenza virus may emerge with the capacity for sustained human-to-human transmission, possibly triggering a pandemic similar to what occurred in 1918, 1957, and 1968.

The tragic events of September 11, 2001, and the deliberate release of anthrax in the Nation's capital, drove home the realization that certain deadly pathogens, such as smallpox or anthrax, could be used deliberately as agents of bioterrorism against the civilian population—similar to radiological, nuclear, and chemical threats. Research in these arenas is critical to meeting these threats, and $1.7 billion is included in fiscal year 2009 budget for such NIH-supported research.

Efforts to prevent, detect, and treat disease require better understanding of the dynamic complexity of the many biological systems of the human body and their interactions with our environment at several scales—from atoms, molecules, cells organs, to body, and mind. As the questions become more complex, and even as knowledge grows, research itself becomes more multi-faceted. We recognize that to effectively push science/new knowledge forward, researchers and scientists must begin to work more collaboratively to develop unifying principles that link apparently disparate diseases through common biological pathways and therapeutic approaches.

Today, and in the future, NIH research must reflect this new reality. Advanced technologies, including sophisticated computational tools, and burgeoning databases, need to be more widely shared with easy public access. The scale and intricacy of today's biomedical research problems increasingly demand that scientists move beyond the borders of their own disciplines and apply new organizational and interdisciplinary models for science. One of NIH's most pressing challenges is to help generate and maintain the trained and creative biomedical workforce necessary to tackle the converging and daunting research questions of this century.

Many of our public health problems have a behavioral component. To put evidence-based interventions into place, all of society must participate. To confront obe-

sity, NIH researchers must continue to address a multitude of intersecting factors, from inherent biological traits that differ among individuals, to environmental and socioeconomic factors and behavioral factors that may have molecular and environmental influences. NIH developed innovative intervention programs such as the WE CAN (Ways to Enhance Children's Activity and Nutrition), now in several hundred communities. WE CAN is designed to help children maintain a healthy weight by promoting improved food choices, increased physical activity, and reduced screen time.

NIH's primary mission is to develop new knowledge in biology and behavior and to apply this knowledge for the benefit of all. NIH is taking a more proactive role in helping to translate these discoveries into practice. For example, we have engaged in the most profound reform of translational and clinical research in the United States in over 50 years. The NIH Common Fund (CF), a new clinical and translational science program, now supports 33 academic centers of excellence charged with the dual task of translating research from the laboratory to patients and discovering the most effective ways of implementing what we know best at the community level. Success in these endeavors depends heavily on our ability to train a new generation of clinician-scientists steeped in modern methodologies and concepts of basic and translational research. This new generation of researchers must be able to work seamlessly with basic and applied scientists in an interdisciplinary environment.

Through our ICs, NIH conducts many comparative effectiveness trials that provide evidence for more effective strategies of care. Many similar NIH-supported comparative effectiveness trials are uncovering evidence that shows, for example, that older generic drugs can often be as effective as newer medications in the treatment of high blood pressure (ALLHAT trial), or certain mental health disorders (CATIE trial). In order to disseminate these results, ALLHAT investigator-educators made 1,696 presentations to 18,905 clinicians in 42 States and Washington, DC.

Given the structure of our healthcare system, it is often difficult for providers to implement the evidence from these large NIH trials. This challenge is real and requires that all relevant parties work collaboratively toward a more systemic approach that goes beyond simply conducting more research of this type. All healthcare components must come together to develop clear follow-through mechanisms to implement the evidence generated by these large trials.

OUR NATION MUST SPUR INNOVATION

With the NIH Reform Act of 2006 (Public Law 109–482), Congress provided a foundation for the centerpiece of the NIH Common Fund (CF) for Medical Research that provides "incubator space" to spur innovation. The CF supplies a centralized source of funding for trans-NIH initiatives to meet the research and training needs of the 21st century and stimulate innovation. Research initiatives supported by the CF must not only be trans-NIH and fill a gap in our knowledge base but also be potentially transformative. The CF invests in systems biology, interdisciplinary research, biocomputing, and clinical research, all of which are fundamental to moving biomedical research forward expeditiously. The budget request includes $534 million for such activities.

The Human Microbiome project is one such initiative. It promises to reveal how bacteria and other microorganisms that are found naturally in the human body (the "microbiome") influence a range of biological processes, including development, immunity, and nutrition. This effort will not only improve our understanding of how an individual's microbiome relates to disease, but will also support the development of new technologies and computational approaches—all cross-cutting outputs that can be applied to investigations of other biosystems.

Another new initiative at the biomedical research frontier is the NIH Epigenomics Program. It will scan the human genome to study heritable features that do not involve changes to the underlying DNA sequence, but significantly affect gene expression and inform us about how DNA is regulated. This analysis of epigenetic changes should reveal new cellular pathways and mechanisms that influence disease progression. Also, the CF continues to support other important initiatives, such as the Pioneer Award program for $36 million in fiscal year 2009 which nurtures high -risk ideas that, if successful, can have unusually high scientific impact.

Nurturing a new generation of innovators is critical to our future research endeavors. NIH makes strategic investments at every point in the pipeline to improve the flow of talent drawn from every part and population of America. We produce teaching supplements to help educators in grades 2 through 12 convey difficult concepts through engaging activities, improving health literacy, and hopefully sparking children's interests in careers in research. NIH offers undergraduate students re-

search experiences, especially geared toward tapping the vast potential of young people from historically underrepresented groups in the sciences.

NIH grants fund graduate students and post-doctoral fellows, who go on to fill most every niche in the American biomedical research enterprise—from academic research to private industry, and from venture capitalists to policy makers. But most importantly, young people need to see, at all stages of the pipeline, that biomedical research is an attractive career. They need to see that there is a stable research enterprise, providing them opportunities to explore their best ideas for improving human health. The budget request includes $123 million for individual fellowship awards under the Ruth L. Kirschstein program.

NIH-supported scientists continue to discover the fundamental underpinnings of human biology in all of its complexity through investigator-initiated research, the mainstay of creativity in science. Thus, one of the top budget priorities is to sustain the number of competing Research Project Grants (RPGs). The budget funds essentially the same level of competing RPGs in 2009 as estimated in 2008—about 9,760 RPGs at $3.5 billion. Overall, NIH will support nearly 38,260 RPGs at $15.5 billion. This was accomplished, in part, by holding down inflationary increases for existing and new grants.

One example of our efforts to sustain the research enterprise is the Director's Bridge Awards, which funded 244 scientists in 2007. It preserves the U.S. investment in investigators, laboratories, and the research projects that support our mission. We expect to continue this successful approach in 2009.

Our priorities continue to focus on maintaining a competitive and viable scientific support system, especially for new and early-career scientists. Our long-term demographic projections show the aging of the Nation's scientific workforce. Unless we take an immediate and substantial proactive stance in protecting early-career scientists, this situation will have a negative and long-lasting impact on our competitiveness and innovation as a Nation. In 2007, we set a goal for the number of new career investigators based on the historic 5-year average of more than 1,500—it was surpassed. This represented a substantial increase in new career investigators over the number in 2006 of 1,353. We plan to continue this commitment in 2008 and 2009.

In 2007 and 2008 we also targeted earlier career stages, such as the Pathway to Independence Awards, supported by all NIH ICs. These awards provide 5 years of support for over 170 postdoctoral trainees a year to encourage risk-taking and independence. NIH plans to fund over 350 postdoctoral scientists by the end of 2008 and continue the program in 2009. The budget request includes $56 million for the New Innovator Awards, which support newly independent scientists with novel ideas and potentially large scientific impact. Scientists must be within the first 10 years of receiving their doctoral degree to qualify. NIH funded 30 awards in 2007 and plans to maintain this promising program.

PEER REVIEW AND TRANSFORMATIVE RESEARCH

Peer review is such a fundamental and critical part of the research process that it requires our constant vigilance. With the increasing breadth and complexity of science, along with the increased number of research grant applications, NIH recognized the need to take a comprehensive look at its review process, and make the necessary changes to strengthen it for applicants and reviewers alike. Although our peer review system is outstanding—and emulated throughout the world—we wanted to make it even better

In June 2007, NIH launched a comprehensive effort to identify information about the review process that could be used to enhance the agency's review system. Extensive input was sought and received from a wide range of stakeholders across the country and at NIH, which led to a comprehensive report released in February 2008 detailing the challenges facing our current system, and proposals for improvement. In June of this year, NIH announced the initiatives it plans to implement that should improve review efficiency and effectiveness. These can be grouped into four core priorities: (1) engage the best reviewers; (2) improve the quality and transparency of reviews with a greater focus on scientific impact while streamlining the application; (3) provide for fair reviews across career stages and scientific fields with a greater focus on early stage investigators and transformative research; and (4) develop a permanent process for continuous review of peer review.

An important component of the new plan is an increased commitment to investigator-initiated high-risk, high-impact research to prevent a slowdown of transformative research, despite difficult budgetary times. I firmly support the need for NIH to invest in such research, even more so in times of restricted budgets. Exam-

ples are already under way such as the NIH Director's Pioneer award, the New Innovator Award, and the recently piloted EUREKA award program.

To further stimulate this critical arena of research, NIH intends to continue to grow the Transformative Research portfolio. A key element in this portfolio will be the newly established investigator-initiated "transformative" R01 program, funded within the NIH Roadmap. Potential impact and innovation will be the primary criteria for success in a review process that is designed to encourage risk-taking to achieve revolutionary results. At the same time, NIH plans to continue the commitment for NIH Pioneer and New Innovator Roadmap awards and expand the current EUREKA awards to more ICs in the coming year. Taken together, these programs will represent a substantial investment in investigator-initiated transformative research.

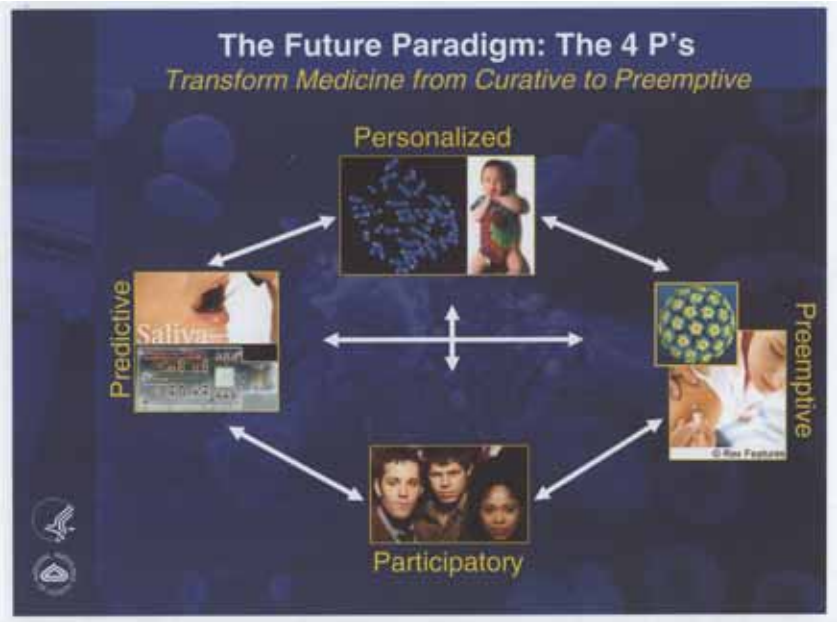
SUMMARY

At NIH, building toward the future involves innovations in multiple areas. We are in the midst of an explosion of new discoveries and novel opportunities for progress across all areas of science—from the most basic discoveries, such as the sequencing of the human genome, to the development of fields—like nanotechnology—that did not exist a few years ago. These advances have dramatically expanded the scope and capacity of the Nation's research enterprise, a goal and outcome of the doubling of the NIH budget.

This remarkable growth in research capacity was accomplished, in part, by leveraging NIH and private sector resources to nurture more investigators, develop new technologies, and build infrastructure. The Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR) programs, help entrepreneurs, as they translate science to market products to improve health and help maintain American economic leadership. A total of 4,350 new technologies were brought to market by 189 universities, hospitals, and private research institutions from 1998 through 2006. From 1980 to 2006, a total of 5,724 new companies were formed around technologies developed by research institutions, many directly funded by NIH.

The United States is now the pre-eminent force in biomedical research. Our Nation continues to lead the highly competitive biotechnology and pharmaceutical sectors. Yet, we are also the focus of increasing competition from growing research in Europe and Asia. NIH programs produce steady streams of novel discoveries and innovative researchers that flow into our industries, making them more competitive. We must continually sustain the momentum of U.S. biomedical research, or risk losing it. Complacency is unacceptable!

We stand today at a crossroads in our efforts to improve health. Healthcare costs are rising. As a society, we must commit to moving forward and capitalize on the momentum created by advances in science and technology. We need to sustain this momentum. Progress in the life sciences in this century will be a major determinant of our Nation's health, its competitiveness, and its standing in the world. This is truly a race against time—a race that we cannot afford to lose.



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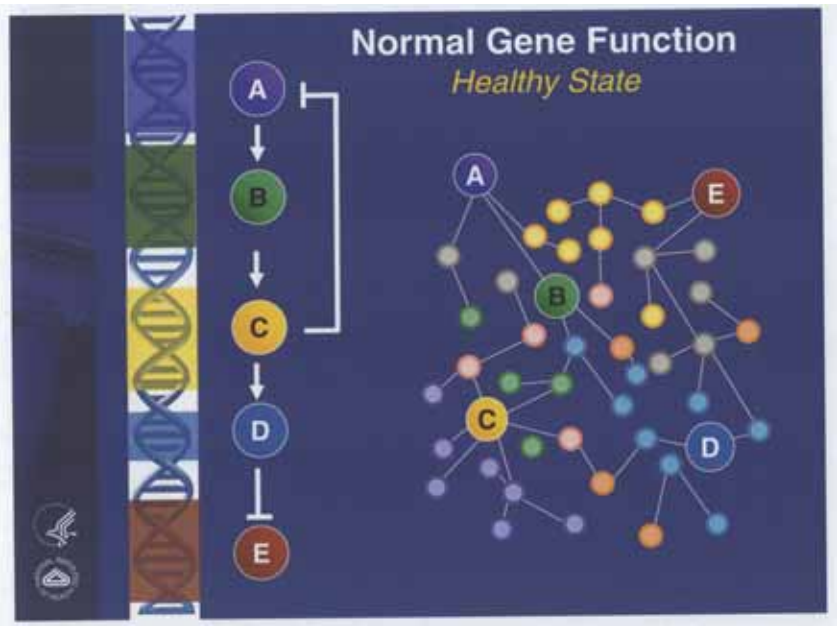

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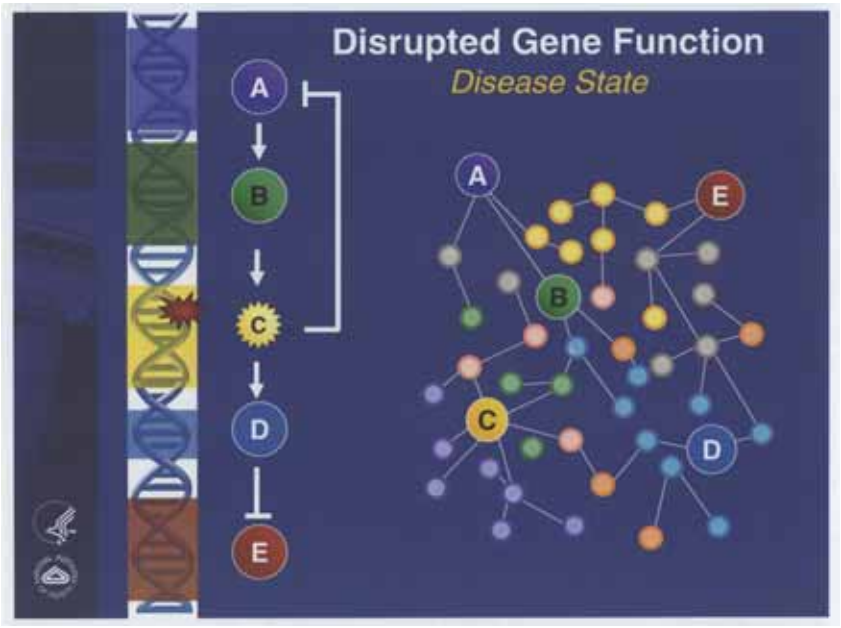

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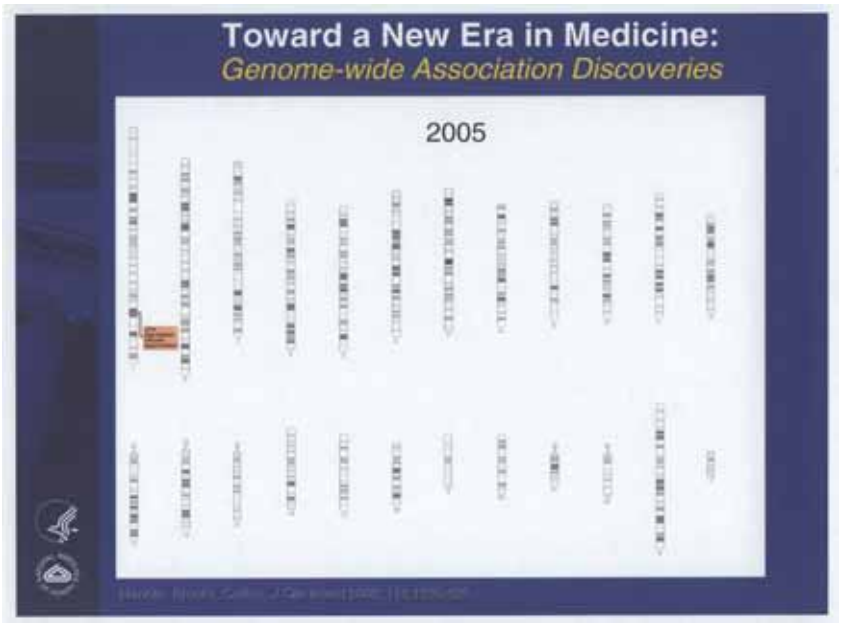

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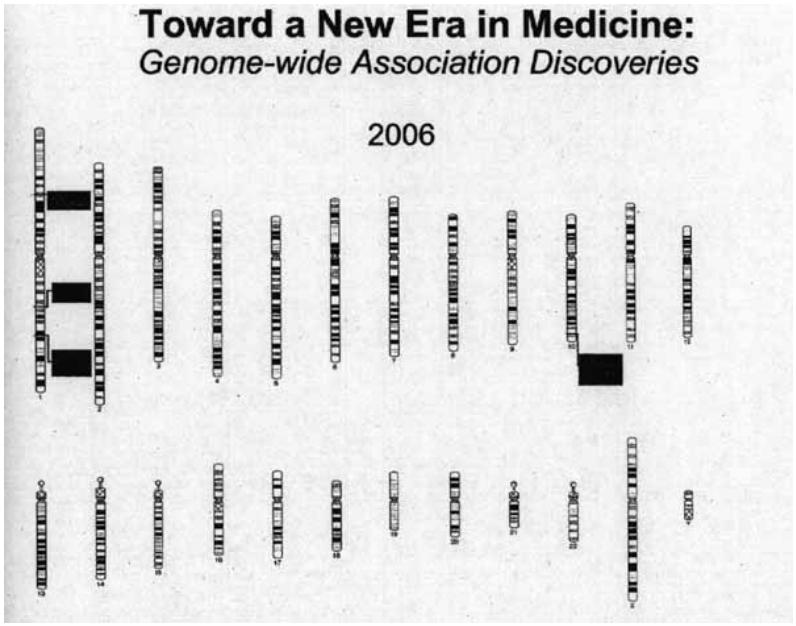

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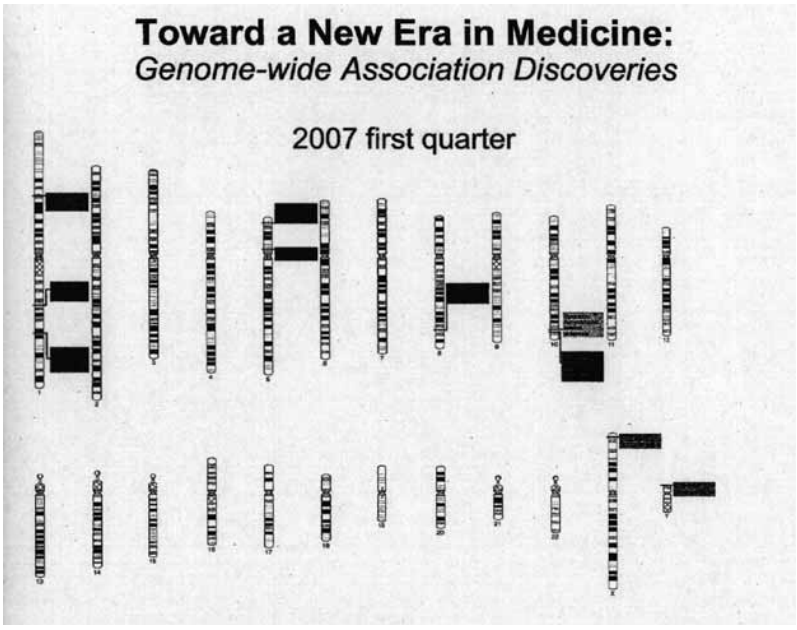

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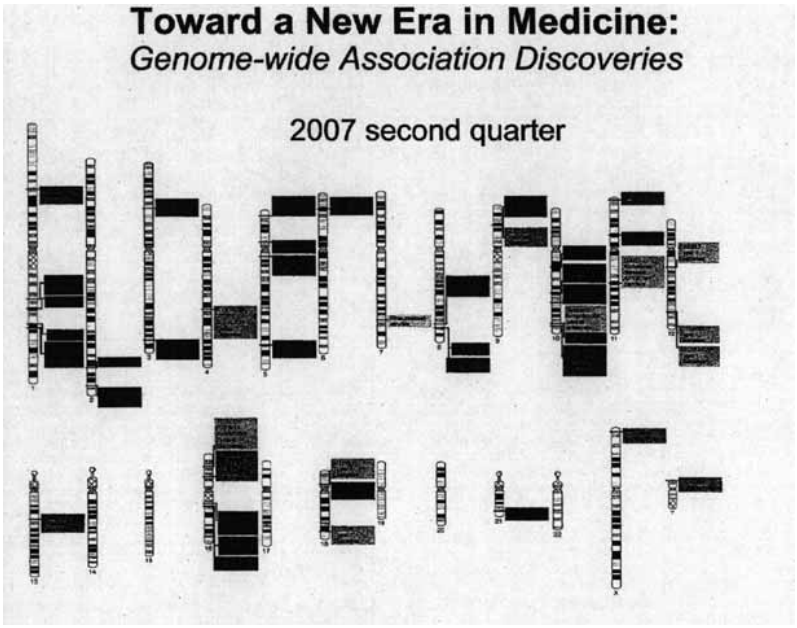

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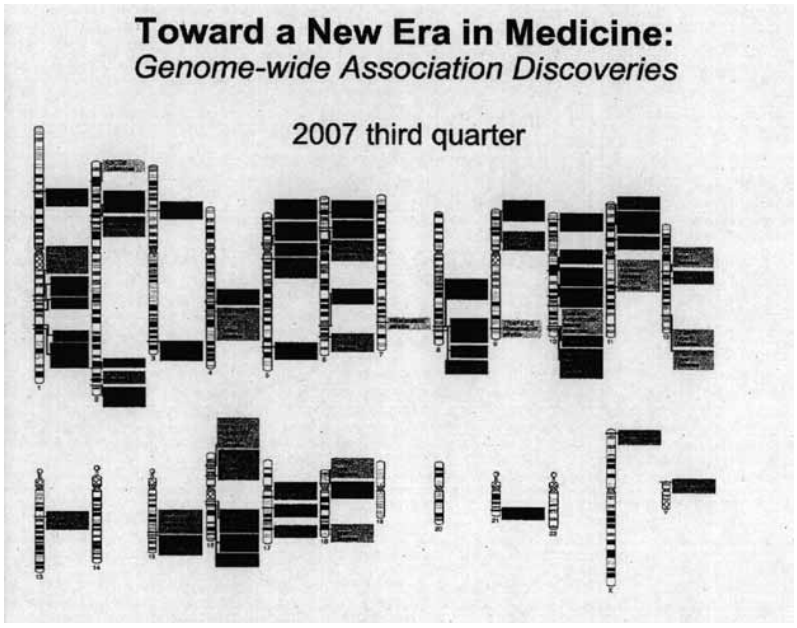

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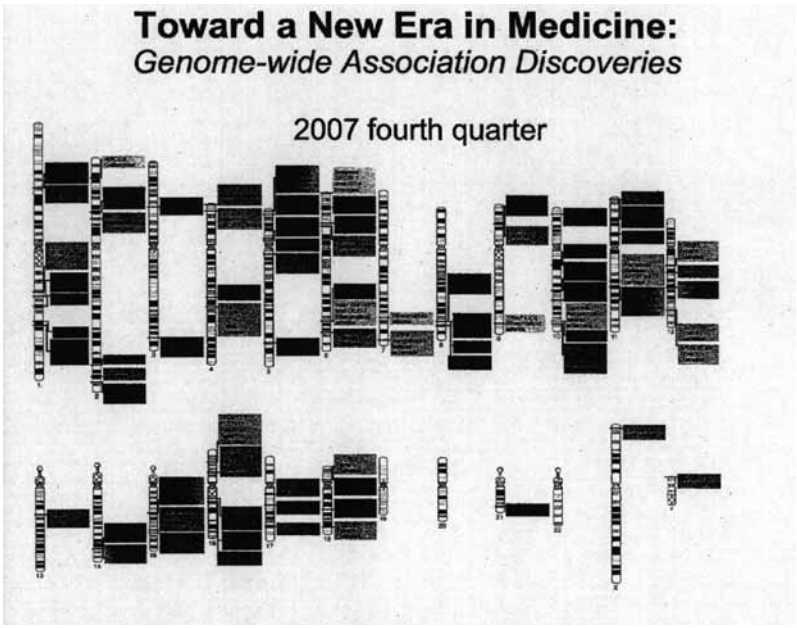

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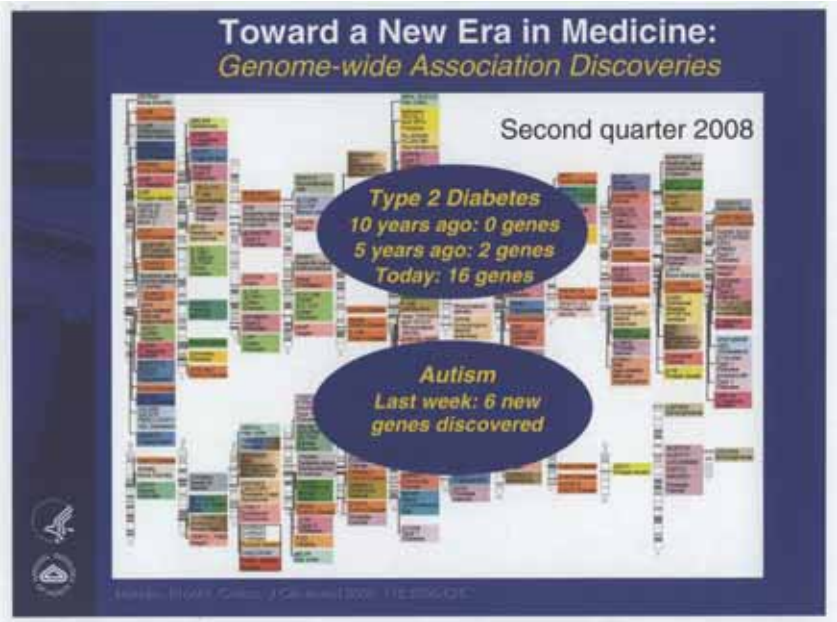

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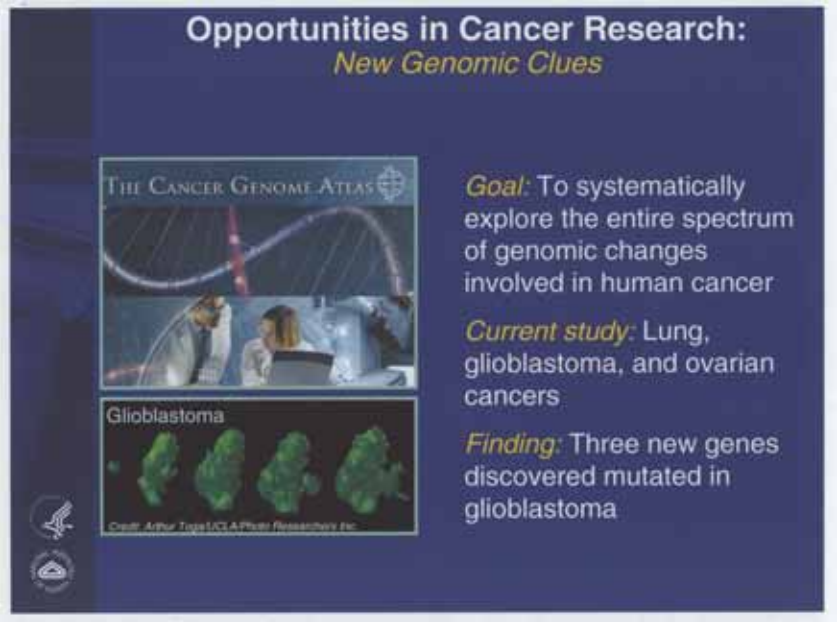

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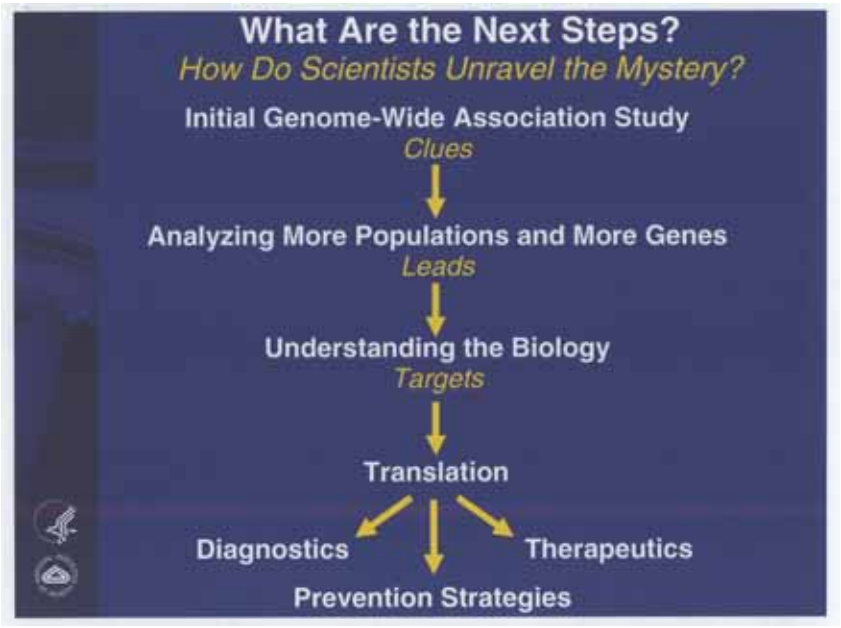

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PREPARED STATEMENT OF DR. ELIZABETH G. NABEL

Mr. Chairman and members of the committee: I am pleased to present the President's budget request for the National Heart, Lung, and Blood Institute (NHLBI) of the National Institutes of Health (NIH). The fiscal year 2009 budget of $2,924,942,000 includes an increase of $2,830,000 over the fiscal year 2008 appropriated level of $2,922,112,000. The NHLBI provides leadership for a visionary and highly productive research program in heart, lung, and blood diseases. In December 2007, the Institute announced a new strategic plan to guide its next decade of research, training, and education to reduce the burden of the diseases under its purview. This statement describes the main elements of the plan and then focuses specifically on the Institute's many efforts to forge a scientific basis for a more personalized approach to medicine in the future and to translate research into practice.

THE NHLBI STRATEGIC PLAN

Thanks to the dedicated involvement of the communities it serves, the NHLBI recently completed development of a scientific working plan to guide its activities and initiatives in the near future. The plan outlines goals that broadly reflect complementary and interactive avenues of scientific discovery—basic, clinical, and translational research. This crosscutting, versus disease-specific, approach highlights areas where the NHLBI is well positioned to make major contributions through investigator-initiated research and through programs that enable and supplement investigator-initiated activities. Shaping the Future of Research: A Strategic Plan for the National Heart, Lung, and Blood Institute is available on the NHLBI Web site at http://apps.nhlbi.nih.gov/strategicplan/, and printed copies have been distributed widely.

In the area of basic research, the plan focuses on delineating normal and pathological biological mechanisms and exploiting the emerging understanding of them to identify biomarkers of disease. Such biomarkers—broadly defined as measurable indicators of genotype, normal or pathological processes, or responses to therapeutic intervention—will facilitate identification of disease subtypes and point the way toward new molecular targets for diagnosis, treatment, and prevention.

The plan's clinical and translational research goals emphasize transmission of knowledge between basic and clinical research so that findings in one arena rapidly inform and stimulate research in others. More precise methods of diagnosing disease

and predicting susceptibility and prognosis are expected to arise from application of new approaches from basic science laboratories. A critical challenge will be to develop individualized preventive and therapeutic regimens based on genetic makeup in combination with developmental and environmental exposures. Insights are already emerging, but robust and efficient means of validating both patient-focused and population-based treatments will be needed to establish an evidence base to guide medical practice.

The plan acknowledges the need to enhance understanding of the processes involved in translating research into practice and to use that understanding to enable improvements in public health and stimulate further scientific discovery. It places particular emphasis on conducting research on primary prevention and identifying interventions that work in real-world health-care practice. As well, continued development and evaluation of new approaches to communicate research advances to the public is an important priority for ensuring full and informed participation of individuals in their health care.

SETTING THE STAGE FOR PERSONALIZED MEDICINE

Considerable progress has been made in reducing the burden of illness, particularly in the area of cardiovascular diseases, through development of therapeutic and preventive strategies that are broadly applicable to the general population at risk. Now we have advanced to a point where it may soon be possible to develop vastly more sophisticated approaches tailored to individuals. The dream is to be able to prevent disease entirely and, short of that, to be able to offer each patient a precisely targeted drug or other intervention, at a carefully titrated dose, for exactly the proper duration, without risking dangerous or troublesome side effects. One path to realization of this dream lies in developing a more complete and detailed understanding of the genetic basis of individual health and disease.

Technological advances that make it possible to identify millions of DNA sequence variations rapidly and inexpensively, and to correlate them with individual characteristics and health indicators (phenotypes), have fueled an explosion of interest in this area. The NHLBI is investing substantial resources to move the science along, capitalizing on vast amounts of data gathered over many years from cohort studies such as the landmark Framingham Heart Study. In 2007, the Institute conducted genotyping using about 550,000 SNPs (single-nucleotide polymorphisms, which are tiny variations in the DNA code) in over 9,300 people from three generations of Framingham study participants. The genetic data are being linked to an array of phenotypic information, including major risk factors such as blood pressure, serum cholesterol, fasting glucose, and cigarette use; biomarkers such as fibrinogen and c-reactive protein; electrocardiography measures; imaging measures that reveal nascent pathology; and data on clinical cardiovascular disease outcomes. The resulting research resource, known as the Framingham SHARe (SNP Health Association Resource), is being developed and maintained by the NIH National Center for Biotechnology Information in its Database of Genotype and Phenotype (dbGaP). This rich source of data will be made available—with appropriate privacy safeguards—to qualified investigators at no cost.

The Framingham SHARe is only the first of many NHLBI efforts to enable what are known as genome-wide association studies (GWAS)—projects that involve scanning markers across complete sets of DNA from many individuals to find genetic variations associated with diseases or conditions of interest. The Institute is moving rapidly to increase the diversity of its genotype-phenotype data resources. Thus, we have created the MESA SHARe, based on cohorts from the Multi-Ethnic Study of Atherosclerosis, a long-running multicenter study that includes Americans of African, Chinese, Hispanic, and European ancestry. The SHARe-Asthma Resource project or SHARP is conducting a genome-wide analysis in adults and children who have participated in NHLBI's clinical research networks on asthma. The Candidate-gene Association Resource or CARE project includes plans to genotype one million SNPs in African-American men and women and link the results with phenotypic data obtained from eight major epidemiological studies, including the Cooperative Study of Sickle Cell Disease and the Sleep Heart Health Study. The NHLBI has also undertaken genotyping of African-American women who participated in the Women's Health Initiative, a project of great interest to many NIH components and the communities they serve.

The GWAS approach offers a powerful and unprecedented avenue to unravel the contribution of complex traits to common diseases, and it is clear that the richness of the data generated from these studies is far greater than could be explored by a single investigator or group of investigators. To ensure that the greatest possible public benefit accrues from our investment in GWAS, under terms and conditions

consistent with the informed consent provided by research participants, the NIH has established a GWAS data-sharing policy for NIH-supported investigators (http://grants.nih.gov/grants/gwas/). I was pleased to lead my NIH colleagues in this effort and, now, I am honored to serve as co-chair of the NIH Senior Oversight Committee for GWAS studies. I believe that robust NIH leadership in all aspects of GWAS will enable a superior yield from this exciting approach and bring us closer to realizing the dream of personalized medicine.

PHARMACOGENOMICS MOVES CLOSER TO THE BEDSIDE

The long-term vision of creating a broad selection of custom-made therapies for individualized treatment is tantalizing, but a great deal of work needs to be done before it can be achieved. Much closer to near-term application is the use of pharmacogenomics—an understanding of how genetics explains individual differences in response to drugs—to guide prescribing decisions for agents currently on the market. A case in point is the use of the anticoagulant warfarin, a tricky drug to prescribe because too little or too much can produce serious problems and the dose requirement varies widely from one patient to another. Research has identified two specific genetic variations that appear to account for much of the inter-individual variation in sensitivity to warfarin, and we are now moving forward with a clinical trial to evaluate the clinical efficacy of a genotype-guided prescribing strategy for warfarin therapy and to determine whether the increment in efficacy and safety warrants the cost of genetic testing. We fully expect that genetic stratification of patients will become the norm for trials to evaluate new drugs, and that genetic information will prove invaluable for the design of novel alternatives to existing drugs that are likely to be ineffective or harmful in genetically susceptible individuals.

BRIDGING RESEARCH AND PRACTICE

In the upcoming years, these and other research efforts will yield an extraordinary amount of new information that will fundamentally transform medical practice and call for innovative approaches to translation and dissemination. We must be prepared to make the most of it. In line with its strategic plan, the NHLBI has developed a new knowledge network approach to bridge the gap between discovery and delivery, identify areas that should be addressed by future research, and develop more effective approaches for synthesizing and organizing scientific evidence and moving it into practice. The first network, addressing cardiovascular diseases, will be implemented globally and make innovative use of new media technologies.

The NHLBI has also begun a new effort to develop comprehensive, evidence-based, integrated guidelines to assist primary care physicians in helping adult patients reduce their risk of cardiovascular diseases. The integrated approach will focus on all cardiovascular risk factors to reflect the complicated clinical scenarios that patients and physicians typically face. Expert panels are being convened to review available scientific evidence and update existing guidelines for the prevention, detection, evaluation, and treatment of high cholesterol, hypertension, and overweightness/obesity. An important goal of both the integrative guidelines and the updates is to improve implementation, especially among high-risk and minority communities. Ensuring that the public benefits from its investment in biomedical research is, and has always been, our highest priority.

PREPARED STATEMENT OF DR. JOHN E. NIEDERHUBER

Mr. Chairman and Members of the Committee: Thank you for the opportunity to offer testimony on behalf of the National Cancer Institute (NCI) and the National Cancer Program. The fiscal year 2009 budget of $4,809,819,000 includes an increase of $4,731,000 over the fiscal year 2008 appropriated level of $4,805,088,000.

A UNIQUE NATIONAL RESOURCE

At his hometown hospital, the patient remembers, "there were lots of debates and lots of questions about what I really had. They really didn't know." His condition was rare, and its identity remained elusive. Ultimately, one doctor made a simple promise: "I'm going to find somebody in this country that knows a lot more about this." And so he did. Ten years ago, the patient headed to the National Institutes of Health Clinical Center in Bethesda, Maryland and a research study lead by Dr. Wyndham Wilson at the National Cancer Institute. The condition turned out to be Lymphomatoid Granulomatosis, a rare, progressive disorder of the lymph nodes and blood vessels that can, over time, involve the lungs, skin, kidneys, and central nerv-

ous system. "If you look at the published literature on my disease," the patient says, "it's a very high mortality rate. What the NCI's treatment regimen has done is completely turn that around. They're doing things that other people just aren't doing, and then sharing it and disseminating it throughout the world." The patient remained in remission for 9 years. Last fall, when his disease returned, the patient returned to Dr. Wilson's care with his optimism intact. "These people at the NIH are so talented, so kind—and they're doing this just to help people and advance learning so that other people can benefit from their work around the country. They're an amazing group of people."

Our patient's cancer story is not finished. Neither is the work of the National Cancer Institute. The NCI is striving for a time when the life stories of millions of patients will no longer end with cancer. For several years now, scientists who devote their careers to the study of cancer have spoken, with increasing frequency and enthusiasm, about their hopes for an era of "personalized medicine," when cancer will be treated as a chronic condition—not the killer it is today. Spurred by the completion of the landmark Human Genome Project, we have begun to realize a vision of cancer prevention, early diagnosis, and targeted treatment based on each patient's tumor and unique genetic make-up. In time, this knowledge will be linked to cancer risk and the earliest cellular changes that lead to development of a malignancy—years before tumor formation or symptom onset.

Today, cancer researchers are using new molecular technologies, such as whole genome scans and actual sequencing of patients' tumors, searching for abnormal proteins in individual patient's body fluids that are the result of these genetic changes. As a result, scientists are studying an ever-growing group of targeted therapies, which attack cancer cells but leave healthy tissue untouched.

Scientists have also learned the critical importance of the microenvironment of tissue surrounding the tumor, and they have elucidated the essential ways in which these cells—connective tissue cells, new blood vessel cells, and cells of the immune system—support the growth and metastasis of the cancer. Scientists have increasingly identified ways in which these non-cancer cells can also be targeted, to block tumor progression. Recognizing the complexity of a cancer and of its progression to a fatal disease, researchers have come to the understanding that our treatments will not be simple; complex therapies will help fight a complex disease. Without a doubt, science and the technology that supports research are making progress against cancer at a pace never before seen.

America's Federal investment powers—and empowers—the engine of cancer research. The National Cancer Institute, as the leader of our National Cancer Program, funds thousands of researchers (5,713 in 2007) at hundreds of our great research universities and Cancer Centers from coast to coast—along with a cadre of Government scientists based at the clinical center on the campus of the National Institutes of Health who, like Wyndham Wilson, conduct the kind of high-risk science unlikely to be found elsewhere.

Clearly, the Nation's investment is paying dividends. There are now almost 12 million cancer survivors in America. Today's cancer research shows great promise to reduce the personal and financial costs associated with cancer, which, according to the American Cancer Society, totaled $206.3 billion in the United States in 2006. However of great worry, cancer is a disease of aging, the result of a lifetime of genetic alterations, additions, and subtractions that accumulate in our genes and impact their function. With a rapidly aging population, NCI estimates that the total economic burden of cancer in the United States will increase to $1.82 trillion by 2017.[1] This clearly underscores the urgency of increasing our investment in cancer research.

NCI's progress against cancer is evident across its vast research portfolio:

—Genome-wide association studies are revealing increasing numbers of genes that may contribute to cancer risk. These high-tech studies compare large groups of people: one group with a disease and one without, searching for abnormal genes, which, once validated and further studied, will lead to strategies for prevention, enhanced early cancer detection, and novel highly targeted treatments.

—The NCI Community Cancer Centers Program, now in a 3-year pilot phase at 16 sites across the country, is studying how best to bring state-of-the-art, multispecialty cancer care, electronic medical records, and early-phase clinical testing of new therapies to patients in their own communities, because access to scientific advances is an essential factor in decreasing cancer mortality and healthcare costs.

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[1] National Cancer Institute, Estimates of the National Economic Burden of Cancer for 2007 and 2017, April 17, 2007.

—The cancer Biomedical Informatics Grid (caBIG™) is a 21st century information initiative connecting cancer research and clinical trials—both public and academic—from coast to coast. caBIG is an essential program to address the new era of highly personalized medicine and the rapid translation of discovery to practice.
—Expanding deployment of Electronic Health Records linked to clinical research can provide security and portability for patient health and medical information.
—Pioneering a new kind of early clinical trial, which looks at small numbers of patients and uses extremely small quantities of investigational medications and high-technology imaging, to see if the drug reaches its molecular target. Phase 0 trials have the potential to shorten drug development and reduce costs by millions of dollars.
—NCI's expanding platform of new drug development actively links university scientists with the complex enterprise of novel agent chemistry, validation, and the final steps of private sector translation.

CANCER AS A MODEL OF DISEASE

Cancer has long been a model for the study of disease in the laboratory and a model of healthcare in the community. For example, knowledge about how tumors form new blood vessels (angiogenesis research), has contributed to our understanding of macular degeneration, diabetes, wound healing, and ischemic heart disease. In fact, the Nation's investment in cancer research has affected the diagnosis and treatment of most major diseases. Cancer is the only disease for which tissue is routinely collected for study in the laboratory. Having malignant, pre-malignant, and normal tissue from the same patient allows researchers in many fields to understand the biology of pathologic disease processes, at the cellular level. The ability to perform tissue analysis also makes cancer patients the most highly characterized population of patients with chronic disease. Physicians are now using these data to inform prevention and treatment schemes tailored to the individual. The NCI recognizes that characterizing the patient and delivering state-of-the-art care in the community setting is the model for future healthcare delivery. We are continually studying ways to optimize this approach.

SUPPORTING RESEARCH

The backbone of America's cancer research enterprise is the individual investigator working at a laboratory bench, conducting hypothesis-driven science. These scientists are also the academic faculty who train and guide the next generation of researchers. Understanding those dual values, NCI is working to reassign resources to provide a stable level of financial support for Principal Investigators.

NCI is also pushing to reinvigorate its intramural program, comprised of the Government scientists who study types of cancer unlikely to be addressed by the private sector and whose research encompasses high-risk science that has the potential to greatly advance our knowledge of cancer and its processes.

One of the greatest services NCI can offer the Nation is to help foster a dedicated cancer research workforce for the future. We have placed more emphasis on carefully reviewing and more-aggressively funding new applications from young scientists. We are working to bring more young scientists to Bethesda for day-long meetings and interactions with NCI staff. Moreover, because a grant from NIH is often a pre-requisite for obtaining and keeping academic tenure, NCI is developing plans to mandate a mentoring committee at each new investigator's home university.

WORKING FOR PATIENTS

When she arrived at the NIH Clinical Center, our patient couldn't even make a fist. Her hands, wrists, elbows, hands, and knees could scarcely bend. A once-vibrant woman in her late 20s, she was now severely anemic, wheelchair bound, and wrapped in blankets to preserve the body heat her skin could no longer retain. Over 2 years, as she suffered the disabling manifestations of cutaneous T-cell lymphoma, she spent more nights in the hospital than at home. She was in hospice care and lacked the strength to be with her two small children. She came to the Clinical Center virtually out of treatment options—and once there, an initial short list of experimental treatments had all failed. Having apparently run out of all hope, our patient came into the care of Dr. Martin E. Gutierrez, a staff clinician with the NCI's Medical Oncology Branch. Dr. Gutierrez, who has spent his career working on new therapies for T-cell lymphoma patients, tried a new drug being developed through NCI's Rapid Access to Intervention Development (RAID) program. RAID exists to speed the translation of novel anticancer therapies from laboratories to patients.

And in this case, the new drug paid off dramatically. Within the first few doses, Dr. Gutierrez began to see improvement. Within 7 months, the patient's symptoms were gone. Today, more than a year after her arrival at the Clinical Center, the patient's tests show no evidence of disease.

NCI will not rest until such stories are commonplace. Our Nation's investment in cancer research is paying dividends—in lives saved, in greater quality of life for cancer patients, and in cancers prevented. The National Cancer Institute is dedicated to a future in which cancer is no longer the killer we know today, but a condition most often prevented, or else treated effectively, with minimal side-effects. The future of medicine is personal. Our country's investment in that future is vital. Everything we do at NCI begins and ends with real people: those with cancer, those at risk for the disease, and those who care for them.

PREPARED STATEMENT OF DR. FRANCIS S. COLLINS

Mr. Chairman and Members of the Committee: I am pleased to present the fiscal year 2009 President's budget request for the National Human Genome Research Institute (NHGRI). The fiscal year 2009 budget includes $487,878,000; an increase of $1,099,000 from the fiscal year 2008 enacted level of $486,779,000.

NIH's investment in the Human Genome Project (HGP) and the International HapMap Project have moved us closer to a future that uses genomic information to diagnose, treat, and prevent disease.

DISEASE-GENE ASSOCIATIONS

The HapMap has introduced a new paradigm to genomic research, primarily in the form of genome-wide association studies (GWAS), enabling cost-efficient assessment of much of the common genomic variation within an individual. The GWAS approach is novel in that it surveys the genome comprehensively and without preconception as to the relationships between genetics and disease, whereas earlier research efforts were largely focused on candidate genes thought to be associated with specific diseases. The innovative GWAS approach allows for the identification of genes involved in common diseases, contributing to a better understanding of the development and progression of common diseases, and pointing to follow-up research that may lead to improved diagnostic, therapeutic, and preventive approaches.

With unprecedented speed, researchers have applied GWAS to identify a stunning number—over 70 in 2007 alone—of genetic factors associated with the most common causes of morbidity and mortality in the United States, such as diabetes, cardiovascular disease, obesity, cancer, and multiple sclerosis. Identification of gene variants associated with disease raises the possibility of using genetic testing, in combination with family history information, to identify susceptible, pre-symptomatic subjects for screening and preventive therapies. The pace of disease-gene discovery is likely to accelerate even further over the next 2 or 3 years due to the completion in 2007 of the second-generation map of human genetic variation (Phase II HapMap). This updated and powerful tool allows researchers to identify variations associated with disease even more quickly and accurately.

APPLYING NEW KNOWLEDGE ABOUT THE GENOME TO HEALTH

The NHGRI has increasingly directed the power of its large-scale sequencing program, which fueled the completion of the Human Genome Project, toward the long-range objective of making human DNA sequencing a tool for both research and medical practice. New directions include obtaining genomic sequence data from many individuals with various physical traits and disease states—data that will prove critical for addressing a wide range of questions important for advancing biomedicine. To move these advances more rapidly into clinical care, in 2007 the NHGRI established the Genomic Health Care Branch within its Office of Policy, Communication, and Education. The new branch's mission is to help facilitate the translation of genomic research into advances in clinical medicine, especially in the primary care setting.

THE CANCER GENOME ATLAS

The Cancer Genome Atlas (TCGA) is a joint NCI-NHGRI effort to accelerate understanding of the molecular basis of cancer through application of genome analysis technologies. TCGA began in 2005 with a 3-year, $100 million pilot project to determine the feasibility of a full-scale effort to explore the universe of genomic changes involved in all human cancers.

THE HUMAN MICROBIOME

There are more bacteria in the human gut than cells in the entire human body. Furthermore, microbes in the gut, skin, oropharynx, and vagina have a profound effect on many human physiological processes, such as digestion and drug metabolism, and play a vital role in disease susceptibility and even obesity. The Human Microbiome Project, conducted under the auspices of the NIH Roadmap Project and co-led by the NIAID, NIDCR, and NIDDK, represents an exciting new research area for the NHGRI.

TECHNOLOGY ADVANCES, ON THE WAY TO THE $1,000 GENOME

In August 2007, the NHGRI awarded grants to advance the development of innovative sequencing technologies intended to reduce even further the cost of DNA sequencing and expand the use of genomics in biomedical research and health care. With NHGRI support, excellent progress has been made toward both the near-term goal to lower the cost of sequencing a mammalian-sized genome to $100,000, and the longer-term goal of $1,000 or less. Further grant awards in this area will be announced in late summer 2008.

CHEMICAL GENOMICS AND MOLECULAR LIBRARIES

The chemical genomics initiative, part of the NIH Roadmap, offers public sector researchers access to high-throughput screens to test small organic molecules for potential uses as research tools. This initiative will even help expedite the development of innovative drugs for rare diseases, by demonstrating how early stage compounds interact with novel molecular targets. This program provides direct translation of genomic medicine by identifying small molecule drug-like compounds that can be used as starting points for new treatments, or as new applications of that agent. A dramatic example is the recent identification of a compound that shows great promise for the treatment of schistosomiasis, a parasite disease affecting more than 200 million people in Africa, Asia, and the Middle East.

KNOCKOUT MOUSE PROJECT

The technology to ''knock out,'' or inactivate, genes in mouse embryonic stem cells has led to many insights into human biological processes and human disease. However, information about knockout mice has only been published and made available to the research community for about 20 percent of the estimated 20,000 mouse genes. Recognizing the wealth of information that mouse knockouts can provide, the NHGRI launched a trans-NIH, coordinated, 5-year cooperative research plan that, in cooperation with European and Canadian programs, will produce knockout mice for every mouse gene and make these mice available as a resource to the entire community.

1000 GENOMES

The 1000 Genomes Project is an international research project that will sequence the genomes of at least a thousand people from around the world to create the most detailed and medically useful picture to date of human genetic variation. The 1000 Genomes Project seeks to produce a publicly available catalog of variants that are present at 1 percent or greater frequency in the human population across most of the genome.

CLINSEQ

The purpose of ClinSeq, an intramural NHGRI research initiative, is to pilot large-scale medical sequencing (LSMS) in a clinical research setting and to investigate some of the technical and medical issues that accompany the implementation of LSMS in clinical settings. Currently, ClinSeq is recruiting 1,000 participants across the spectrum of risk for coronary heart disease (CHD). Relationships between patients' genetic makeups and observed phenotypes will be explored to better understand how variations in genes relate to cardiac health status.

MULTIPLEX

The NHGRI and the NCI have teamed up with Group Health Cooperative in Seattle and Henry Ford Health System in Detroit to launch the Multiplex Initiative, a prospective study that is enrolling young, healthy adults to learn how they react to the offer of genetic testing for a panel of 15 genes linked to 8 common conditions. The study will follow individuals who decide to have the testing to see how they interpret and use the results in making future health care decisions. This study

should provide insights that will be important to advancing the realization of personalized medicine.

ENCODE (SCALE UP AND MODENCODE)

We are continuing to expand the ENCyclopedia Of DNA Elements (ENCODE) project, a research consortium that, in its pilot phase, yielded provocative new insights into the organization and function of the human genome. The NHGRI is moving forward with a full-scale initiative which should provide a more comprehensive picture of the biological roots of human health and disease. We are also engaged in a new effort, called the model organism ENCODE (modENCODE), to apply many of the ENCODE methods and technologies to the genomes of the roundworm and fruit fly model organisms, to inform our efforts to understand how the human genome functions.

MINORITY OUTREACH ACTIVITIES AND HEALTH DISPARITIES

The NHGRI remains at the forefront of ensuring that minority scientists and students are equipped to meet the challenges of genome research in the 21st century. With support from the NIH Director and several Institutes and Centers, the NIH has created the NIH Intramural Center for Genomics and Health Disparities (NICGHD) within the NHGRI Division of Intramural Research, with a mission of advancing research into the role of culture, lifestyle, genetics, and genomics in health disparities.

GENETIC DISCRIMINATION

The NHGRI has long been concerned about the impact of potential genetic discrimination on research and clinical practice, as a wealth of research has demonstrated that many Americans are concerned about the possible misuse of their genetic information by health insurers or employers. This concern has been a constant during my tenure as director of NHGRI, so it gives me great satisfaction that after a 13-year legislative effort, the Genetic Information Nondiscrimination Act (GINA) has finally become law. When GINA takes effect in 2009, it will provide all Americans with solid protection against discrimination based on their genetic information in health insurance or employment circumstances. We hope that these protections will address the concerns that have thus far threatened the public's willingness to utilize genetic testing.

MEDICINE IN THE FUTURE

Broad investment in innovative, large-scale, and adaptable models of research such as GWAS may accelerate the timeline for the development of advances in clinical options and thereby contribute to a decrease in the public health burden of many common diseases. With protections against discriminatory uses of genetic information in place, we anticipate that individual genome sequencing will become both commonplace and affordable, and that primary care physicians will routinely consult their patients' genome analyses for prediction of risk, diagnosis, and drug and dosage selections. If the public and the medical community are appropriately educated about both the significance and the limitations of genomic information, it may be possible to lessen the burden of disease through better screening and prevention programs, to minimize or avoid toxicities from drugs, and to select the right drug for the right patient, at the right time.

Finally, as many of you know, next month I will step down as Director of the National Human Genome Research Institute, a position that has been my joy and privilege to hold for the past 15 years. Many historic opportunities lie ahead as genomics increasingly becomes a leading force in medicine, and I leave my position supremely confident that NHGRI and NIH will continue to achieve notable success in advancing the health of the American people. In closing, I would be remiss if I did not take this final opportunity to thank Senator Harkin and Senator Specter for their superb leadership on this committee and long-time dedication to the mission of the NIH. Your efforts, and that of your excellent staff, have been essential to the progress recently made in genomics research, and are very much appreciated.

PREPARED STATEMENT OF DR. ANTHONY S. FAUCI

Mr. Chairman and members of the committee: I am pleased to present the President's budget request for the National Institute of Allergy and Infectious Diseases (NIAID) of the National Institutes of Health (NIH). The fiscal year 2009 budget of

$4,568,778,000 includes an increase of $8,123,000 over the fiscal year 2008 appropriated level of $4,560,655,000.

The mission of NIAID is to conduct and support research to understand, treat, and prevent infectious and immune-mediated diseases. The biomedical research that NIAID supports to combat diseases of worldwide concern, such as HIV/AIDS, tuberculosis, malaria, neglected tropical diseases, emerging and re-emerging infectious diseases, has taken on added importance in today's globalized society. As we address these problems in a global context, we naturally contribute to our country's preparedness against the threat of bioterrorism as well as naturally occurring disease outbreaks. In addition, we are advancing efforts to address other domestic health problems, such as HIV/AIDS, influenza, and asthma, allergy, and other immune-mediated diseases. Using a multidisciplinary approach that engages industrial, academic, governmental, and non-governmental partners, NIAID remains committed both to basic infectious and immune-mediated disease research and the application of this knowledge to the development of strategies to detect, prevent, and treat these diseases. This approach is emphasized in the recently updated NIAID strategic plan, NIAID: Planning for the 21st Century—2008 Update.

Looking forward, it is clear that the research activities of NIAID will become more important than ever, as current and as-yet unrecognized health threats will require new diagnostic, preventive, and therapeutic interventions. These new tools promise to have a great impact on public health over the next two decades.

EMERGING INFECTIOUS DISEASES AND GLOBAL HEALTH

Threats posed by infectious microbes do not remain static, but change over time as new microbes emerge and familiar ones re-emerge with new properties, such as drug resistance, or in new settings. Since 2006, we have witnessed numerous examples of newly emerging and remerging infectious diseases outbreaks, including extensively drug resistant tuberculosis (XDR–TB), methicillin-resistant Staphylococcus aureus (MRSA), H5N1 avian influenza, Chikungunya fever, and dengue. We must anticipate that we will see more and more of these outbreaks in the coming decades. As economies and societies around the world have become increasingly interdependent, responding to emerging infectious diseases, as well as to long-established global health challenges such as neglected tropical diseases, has taken on a new urgency.

Tuberculosis is an example of a re-emerging threat. The World Health Organization (WHO) estimates that in 2006, new cases of active tuberculosis (TB) worldwide exceeded 9 million and 1.7 million people died from TB. Antiquated and insensitive techniques for accurately diagnosing TB, complex and lengthy drug regimens and an increase in the prevalence of multi-drug resistant (MDR-) and XDR–TB continue to present major challenges to effective TB control. In 2007, the Institute released the NIAID Research Agenda: Multidrug-Resistant and Extensively Drug-Resistant Tuberculosis, which identifies research needs and priorities in several critical TB-related areas. The agenda also highlights the importance of fostering partnerships with public and private organizations to fuel the pipeline of available drugs, diagnostics, and preventive measures for TB.

Malaria is an established infectious disease that continues to pose a significant global health burden. Malaria is becoming even more problematic with the emergence of drug-resistant malaria parasites and insecticide-resistant mosquito vectors. NIAID collaborations with public and private partners, including the Bill & Melinda Gates Foundation, build on the foundation of NIAID's robust malaria basic research program to foster the development of promising drug and vaccine candidates. Over the next two decades, we hope to have a major impact on the global TB and malaria burden through the development of vaccines that protect against these infectious killers. Our aim is excellent control of both TB and malaria through the use of vaccines and other interventions with the ultimate goal of eliminating malaria as a global disease threat.

TB and malaria are not the only diseases emerging in drug-resistant forms. The Centers for Disease Control and Prevention estimated that in 2005, more than 90,000 individuals in the United States developed invasive infections with methicillin-resistant Staphylococcus aureus (MRSA) and nearly 19,000 of these patients died. NIAID supports an extensive basic research portfolio on antimicrobial resistance, including studies of how bacteria develop and share resistance genes and the identification of new therapeutic targets. The Institute is partnering with industry, other Federal agencies, academia, and other organizations such as the Infectious Diseases Society of America, to identify research priorities, including clinical trials, to address this growing problem, and recently published a detailed research agenda on antimicrobial resistance in The Journal of Infectious Diseases.

Seasonal influenza, which changes slightly every year, is the classic example of a re-emerging infectious disease. Influenza viruses also can undergo more drastic genetic changes that periodically enable them to evade pre-existing immunity and cause a pandemic, such as the deadly influenza pandemic in 1918 that killed more than 50 million people worldwide. NIAID supports a broad portfolio of research on influenza, including basic and applied research on the development of vaccines, diagnostics, and therapeutics against both seasonal and pandemic influenza. This foundation of research has underpinned the significant progress made in the development of new influenza interventions. For example, in 2007, based on clinical data from NIAID-supported research, the FDA approved the first vaccine for humans against the H5N1 avian influenza virus. Further, NIAID-supported studies performed in collaboration with various industrial partners have demonstrated the extraordinary potential for a variety of other vaccine formulations and adjuvants to not only expand the number of doses of vaccine but also to broaden the vaccine's reactivity against various strains of influenza.

As we look to how we might respond to unknown emerging and re-emerging infectious disease threats in the future, it is apparent that the most practical approach may not always be the development of interventions such as diagnostics, vaccines, and therapeutics against just one microbe. Rather, the future of diagnostics will be rapid, accurate tools that can be used at the bedside or in the field in "real time" to detect a wide variety of pathogens. We are working to develop vaccine platforms that can be easily adapted to different microbes by shuttling the genes for different antigens in and out and that can provide protection against a broader group of pathogens. Similarly, we are developing antimicrobial therapeutics that truly are "broad spectrum" in their activity, both within and between classes of pathogens. Such antimicrobials could prove effective against drug-resistant bacteria, including MRSA.

HIV/AIDS RESEARCH

HIV/AIDS continues to exact a staggering toll. Although the Joint United Nations Programme on HIV/AIDS (UNAIDS) recently revised estimates to indicate a stabilization or decline in HIV infections and deaths in some parts of the world, the HIV/AIDS pandemic remains an enormous global health challenge. An estimated 33.2 million people worldwide are infected with HIV. In 2007, approximately 2.5 million people were newly infected with HIV, and 2.1 million died of AIDS.

Despite the grim numbers, the Federal investment in HIV research has generated promising new results in the prevention and treatment of HIV/AIDS and in advancing our understanding of the virus and disease. An important example is the demonstration by NIAID-supported researchers that medically supervised adult male circumcision reduced by more than 50 percent the risk of heterosexual African men becoming infected with HIV. Our hope is that this and other advances in HIV prevention research will become part of a comprehensive HIV prevention "toolkit" that will markedly decrease new infections over the next two decades.

Perhaps the greatest success story in NIAID-funded AIDS research is that of therapeutics. NIAID-supported research helped make possible antiretroviral therapies that have transformed HIV from an almost uniformly fatal infection into a manageable chronic condition. Still, existing drugs are no longer sufficient for some HIV-infected patients because of the ability of the virus to develop resistance or because of the toxicities that can be associated with the therapies. Among the fruits of NIAID fundamental HIV research is the recent approval of three new potent and highly effective antiretroviral drugs: etravirine, maraviroc, and raltegravir. NIAID will continue to support the fundamental research that will be the foundation for future therapeutics that will be even more user-friendly and inexpensive, making universal access to therapy more feasible over the next two decades.

Prevention efforts continue to be a major component of the HIV research program of NIAID, and the most powerful prevention tool would be a safe and effective HIV vaccine. The development of an HIV vaccine remains one of our greatest scientific priorities, but also one of our greatest scientific challenges. The pathway to a vaccine is being elucidated through the fundamental basic research that remains the foundation of NIAID. For example, researchers at the NIAID Vaccine Research Center and their collaborators determined the atomic structures of a neutralizing antibody and the conserved area of the HIV surface protein (gp120) to which the neutralizing antibody binds. This binding site is the same site that the virus uses to bind to cells of the immune system. Such studies are helping us to identify components of HIV that may serve as targets for future vaccine candidates and may bring us closer to a safe and effective HIV vaccine.

BIODEFENSE RESEARCH

Since the beginning of the acceleration of our biodefense research program in fiscal year 2003, NIAID has achieved a number of successes in the development of countermeasures against significant bioterrorism threats; these countermeasures are either in the Strategic National Stockpile or available for use in an emergency. Promising candidate countermeasures in development include ST–246, a smallpox drug candidate that has protected both rodents and nonhuman primates from an otherwise lethal exposure to live poxviruses. The FDA has granted orphan drug status to ST–246 and awarded the compound fast-track status which will expedite its regulatory review. The vaccine platforms, rapid diagnostics, and broad spectrum antimicrobial therapeutics that we aim to develop for emerging infectious diseases over the next two decades will also be directly applicable to our biodefense research program.

In addition, and as important, NIAID has developed a physical and intellectual research infrastructure that has been critical to our ability to respond to new and re-emerging infectious diseases. Without this expanded infrastructure, the biomedical research response to the emergence of infectious disease threats such as H5N1 avian influenza, MRSA, and XDR–TB would not have been as rapid.

RESEARCH ON IMMUNE-MEDIATED DISEASES

Autoimmune diseases, allergic diseases, asthma, rejection of transplanted organs, and other immune-mediated disorders are significant causes of chronic disease and disability in the United States and throughout the world. NIAID-supported research in immune-mediated diseases has led to significant advances in our understanding of the mechanisms underlying these diseases and in the development of strategies to detect, prevent, and treat them.

Food allergies continue to be a growing concern and an emerging focus of public attention. NIAID remains committed to basic research to advance the understanding of food allergy and food allergy-associated anaphylaxis. To bring new investigators and novel ideas into food allergy research, NIAID is supporting a new initiative, Exploratory Investigations in Food Allergy, in collaboration with public and private partners. NIAID also is expanding support for clinical trials in food allergy, with ongoing trials to prevent the development of allergies to particular foods, such as peanut, and to reverse established allergy to milk, eggs, and peanut.

The Institute also supports research to improve outcomes for transplant recipients, with establishment of immune tolerance as a major priority in this area. The NIAID Immune Tolerance Network is making steady progress towards the long-term goal of reducing the need for costly and potentially risky immunosuppressive drugs that are the current standard treatment to prevent transplant rejection. A total of 11 kidney and liver transplant recipients are no longer on immunosuppressive drugs, some for as long as 4 years. We hope that eventually a substantial proportion of organ transplant recipients will not require immunosuppressive drugs.

The establishment of immune tolerance is a goal not only for transplantation, but also for other immune-mediated disorders, such as allergies. We look forward to the use of tolerance to have a major impact on allergies, including food allergies, and other immune-mediated disorders in the coming decades.

CONCLUSION

For more than six decades, NIAID has conducted and supported basic research on infectious and immune-mediated diseases that has underpinned the development of vaccines, therapeutics, and diagnostics. These, in turn, have improved health and saved millions of lives in the United States and around the world. Through partnerships with industrial, academic, governmental, and non-governmental partners, the Institute will continue to leverage these fundamental discoveries into the tools needed to achieve a healthy world.

Senator HARKIN. Dr. Zerhouni, thank you very much, that was really eloquent and elegant, and I appreciate that very much. I just wondered if—Senator Cochran has joined us, did you have a statement you'd want to make, Senator Cochran?

Senator COCHRAN. Mr. Chairman, thank you very much, I do have a statement that I would ask be included in the appropriate place in the record.

Senator HARKIN. Sure, without objection.

Senator COCHRAN.TThank you.
[The statement follows:]

PREPARED STATEMENT OF SENATOR THAD COCHRAN

Dr. Zerhouni, thank you for joining us today to discuss the fiscal year 2009 budget for the National Institutes of Health. We appreciate your efforts to improve the health of Americans through medical research aimed at the prevention and treatment of diseases. I am pleased that the Committee has provided an increase of over $1 billion above last year's level and I look forward to your comments on the agency's vision and plan for these additional resources. I would also like to welcome our distinguished panel of scientists. The insight you will share today of your experience with the NIH and its research will be helpful to the work of this committee.

The research at NIH addresses the pressing health concerns in our country and it is important not only to complete this research, but to translate it into new therapies and better outcomes for patients. This Committee will continue to encourage you all to do this.

I appreciate the challenges you are facing and your hard work. I am interested in helping the NIH succeed in these very important efforts.

NIH FUNDING

Senator HARKIN. For the record, accompanying Dr. Zerhouni today is, of course, Dr. Francis Collins whom I spoke about in my opening statement, the Director of the National Human Genome Research Institute and Dr. Anthony Fauci, Director of the National Institute of Allergy and Infectious Diseases, who's been at NIH since—is that right, since 1968, Tony? Wow.

Dr. Elizabeth G. Nabel is the Director of the National Heart, Lung and Blood Institute, appointed to that position in 2005, I think, from Dr. LenFont, if I'm not mistaken, who was there for many years.

Dr. John Niederhuber is the Director of the National Cancer Institute.

We thank you all for being here today.

Well, Dr. Zerhouni, just picking up on that, as I said, that very elegant presentation, we think about where we've been, and we're on the cusp of some of these new things, we have to follow these leads. Tell us what that would mean in terms of budgetary implications. In other words, we've got a lot of things we've got to be looking at—I assume this spreads across every Institute, in terms of following these leads. But, what should we be thinking about in terms of the growth in NIH funding? As I said, Senator Specter and I are going to try to introduce a bill to try and get that money back up again, we're facing some pretty tough budget times right now—what should we be thinking about in terms of the funding for NIH next year? The year after, the year after, perhaps, in order to adequately follow these leads?

Dr. ZERHOUNI. There are many ways to answer this question, but I'll give you some parameters I've learned are critical.

You can not sustain an enterprise where you have to have people commit their lives, their careers—it takes 15 years, sometimes, to just make an impact when you're following the lead, this is not automatic. So, these individuals need to have some certainty that the budgets will be there to sustain them in their effort, so predictability in the budget is very important.

SUCCESS RATE

The second is that, you have to have a reasonable success rate. When you tell a young individual, "You will come in, you will come in at age 30, 32, having spent 20 years of your life training yourself, and then you're going to make $40,000 for the next 10 years, and maybe at the end, if you're very, very good, you might get a grant from the NIH with a 17 percent success rate. How does that sound to you?"

Without a 30 percent success rate, on average, we've notice that, fundamentally, our ability to maintain the competitive nature of science, and the ability to explore the avenues—not knowing, really, where the next breakthrough is going to come from. People forget that science is not an engineering task, we don't know all of the answers, we have to seek them. We've done this for 50 years. People forget that the history of true modern research in medicine is only 50 years old. So, we are early in that stage. Losing momentum is very critical.

So, a reasonable success rate, a predictable funding, and funding that does not decrease in real terms—which is what we have had to deal with, which forces you to make priority choices, not knowing, really, where the breakthrough will come from. Because, in science, as we've noted, sometimes somebody is doing something completely unrelated, and all of a sudden, that something becomes a cure in cancer, or that thing in cancer becomes a cure in AIDS. We've seen that over and over again.

So, what is key is to maintain your capacity over time, make sure that new, young investigators are encouraged to enter the career, and make sure that we are not dealing with a very erratic process. Medical research is a long-term process, it's not something you can manage every 12 months. You have to commit.

But we have a plan, we have a strategy. This strategy is known the world over. If we're not following these leads, I can assure you, somebody will. That won't be us.

NEW INVESTIGATORS

Senator HARKIN. Dr. Zerhouni, you have the NIH Director's New Innovator Awards that you have in your office that we provided some money last year for that, $56 million, that goes to new investigators. We included $108 million for the program in our next bill—will that be enough to support the New Investigators Award System? Is this part of bringing, getting these new people in, and getting them started?

Dr. ZERHOUNI. Right, so this is a stop-gap that we have to use, because what my main concern is—and my colleagues know that—is that if you do the projections, and if you don't fund enough scientists today, you won't have them 10, 15 years from now.

So, what we've done—with a lot of hardship—is to shift money into young investigators, new investigators. This needs to continue.

New Innovators was addressing two goals: one is that, once success rates go down, people become very conservative. They don't take chances, they don't take risk into new areas of research, they want to be sure. So, we wanted to encourage risk-taking, and en-

courage new entrants to come in—that's what the New Innovators Awards do.

Our data shows that we really need to fund something around 3,000 new scientists a year to enter NIH. Right now we're below that number, and ideally that would be the goal that we have to have—no matter what the budget does—we need to encourage risk-taking, new ideas, innovation, and new investigators.

FUTURE OF HUMAN GENOME RESEARCH

Senator HARKIN. Thank you, Dr. Zerhouni.

I have questions for all of the panelists, I just have one more question and then I will yield to my colleagues that are here.

Dr. Collins, obviously the presentation this morning that Dr. Zerhouni made is right up your alley. I guess what I'd like to ask you about is again, talk about the future. We've mapped and sequenced the genome, we've now made all these discoveries in terms of the clues—where we do go from here with the Human Genome Project or with the Human Genome Institute? Where do we go from here with that? Tell me about the 1,000 Genomes Project, and what that might mean? Are you supportive of that, is that something that we should be looking at, and trying to support, the 1,000 people that they want to do that on?

Dr. COLLINS. Thank you, Senator. It is my last appearance, officially, as a Government employee in front of this committee, and I would like to express my sincere thanks to you, and to Senator Specter, and to the whole subcommittee for their consistent support and interest in what NIH is doing.

I certainly remember when I first came here 15 years ago, there was a lot of skepticism about whether the Human Genome Project had any chance of succeeding, and it was your support, and that of others Members of the Congress, that saw us through some challenging times, where the technology had to be invented, and people had to be recruited, and a lot of milestones had to be achieved, and the celebration of the accomplishment of those goals in April 2003 is very much a testimony to this Congress and to their vision for supporting this.

Personally, I want to say thank you to you, for all the wonderful conversations we've had through the years about this.

It is a glorious time in genome research, as Dr. Zerhouni's testimony indicated. I've just counted up the number of projects that my Institute is currently managing, going—building on the foundation of having the human genome sequence—there are 19 of them. These are all focused on specific ways in which we can learn from that instruction book, how it operates, and how glitches in the instruction book, our genome, can lead to health or disease.

We are learning a prodigious amount every day. I can tell you, however, that none of those 19 projects are going as rapidly as they could—we are constrained, and not by talent, not by ideas, not by opportunities, but very much by the budgetary abilities that we have to expand on these projects. That is, of course, for me a source of some frustration.

The 1,000 Genomes Project is one of those—this is an international effort, just as many of the genome projects have been. It's rather amazing to be able to say that the people were skeptical

about whether we'd ever sequence one genome, we're now proposing to sequence 1,000 of those, derived from DNA samples from individuals in Europe, and Asia, and Africa, and to have that done in the next 2½ years.

We're doing this in collaboration with England and China, and we're already deep into a pilot project which in its first 3 months of effort generated more DNA sequence data than has ever been generated in the history of the planet, so we're really producing a vast amount of interesting information that's laying out this catalog of human variation at a level of detail not previously imagined possible.

It's going to teach us a lot about how it is that DNA variation plays a role, and who's at risk for what, and that's just one of these 19 projects.

There more that we could be doing, if you'll give me just a moment, I'd like to mention two.

GENES AND ENVIRONMENT

One of the things we really need to understand more about, of course, is how the genetic risk factors interact with the environment.

All of those banners on the diagram that Dr. Zerhouni showed—which are enormously exciting advances, figuring out risk factors for diabetes and heart disease and cancer and asthma—those are, of course, inherited risk factors that you're not going to be able to change in the people who have them. But it is an interaction between those genetic risks and environmental exposures, such as diet, and lifestyle and medical surveillance and whatever's in the air and the water, that determines whether somebody is going to get sick, or not. We could modify those things, if we understood exactly who's at risk, and we could focus on that, in an individualized way. That's what personalized medicine is all about.

But, collecting that data is not trivial. A dream that I've had for the last 4 years, but haven't been able to get off the ground in the current budget climate, is to have a national study of health and disease, collecting information on, perhaps, half a million volunteers from across the country, who would basically agree to have their environmental exposures studied, as well as their medical conditions, and their DNA. If we put that all together, in an organized effort with access to qualified investigators, we would finally, really have a rigorous way of understanding this.

You could call this the American Genes and Environment Study, or AGES, some of us have done that. We've organized a group of more than 60 scientists to think about how to put this together. I have yet to meet somebody who doesn't think this would be an enormously exciting project to undertake, but it's expensive. It's genome project-like in its budget, and at the present time it's been hard to get it off the ground.

RARE AND NEGLECTED DISEASES

That's one. Another one, which I'm enormously excited and optimistic about, is to take the discoveries that we are making about the causes of where neglected diseases, where we are making great

progress and really, in a very intentional way, translate those into treatments.

The NIH has made major investments, particularly through the Roadmap that Dr. Zerhouni has so effectively championed, to put us in the position to do that, and we have many other pieces in place, to take a discovery about a rare disease, and lead it all the way to a clinical trial. In a circumstance where the private sector, understandably, is not going to be very interested in investing, because the market size is going to be quite small. We are only missing on, sort of, major piece here, and an initiative to fill in what's called the Valley of Death, between when you have a promising lead compound, and when you have something you could actually contemplate putting into a patient is something I would be enormously excited about.

We couldn't have really done that 4 or 5 years ago, but we could now. With an infusion of just the right amount of support, I think this is something that we've underlined what we're really about at NIH, which is trying to find cures. Yes, we do great basic science, and we're proud of that, but our goal—as yours—is to take that to the clinic, and do something for patients.

BUDGETARY CHALLENGES

So, I'm excited about all of those things, but again, being my final hearing, I guess I could speak about as bluntly as anybody at the table—I am very concerned about whether we will achieve those kinds of optimistic outcomes, if we can't turn the corner on what has been a very difficult 5 years.

It's been my most difficult 5 years, having to turn away young investigators—some of whom have gone away and won't come back—they've given up. Having seen the way which science that could have gone forward, has been blunted by the inopportunity to jump in and provide those kinds of supports. Having seen a delay in the health benefits that we are all dedicated to achieving, being slowed down by the inability to push forward agendas which, scientifically, are very exciting, but we just can't do it with the current support.

Frankly—as we're also worried about our economic circumstances, seeing how an investment by NIH which various studies have indicated, pays back somewhere between two and sevenfold—isn't happening, either out there in our country, which is where most of our money goes.

Frankly also, as somebody who's worked in the international community, as I've had the pleasure of doing, I'm seeing our leadership on many of these projects eroded by the fact that NIH is not keeping up with what's happening in other countries, including England, and China, and India and that can't be a good thing for our country.

So, I appreciate what you and Senator Specter are doing in this hearing, to highlight the importance of maintaining that kind of support, and perhaps, catching up from what has been a pretty difficult half a decade. If we could turn that corner, keep our investigators who are just on the edge of giving up, inspired that they could actually make a contribution, then I think we could recover a lot of what we're in danger of losing.

Thank you for the extra minutes you gave me to answer that question.

Senator HARKIN. Dr. Collins, thank you very much. Again, for the benefit of members of the subcommittee and perhaps some of the public who may not know these figures, when Dr. Collins took over the Human Genome Project in 1993, I can remember the hearings at that time when I was Chair at that time, and the estimate was that it would take us 15 years, and over $3 billion to map and sequence the human genome. But we did it in 10 years, basically—there's a few little holes that were left over—but basically 10 years, and less than about $2.6, $2.7 billion.

Now, that's important, but there's one other thing that's very important, that I think members ought to know. That it was about that time, about right around 1993, 1994, when there were moves made to take this from the public sector and put it in the private sector. That the Human Genome Project would better be done in the private sector, rather than the public sector. There was quite a battle about that at that time, and I can remember, people said, "Why should we be investing, why should we be investing public money in this when the private sector can do it?"

Dr. Collins was very eloquent at that time, and very forceful, in telling us that, no, this belongs in the public sector. This basic research ought to be available to everyone, and if it's in the private sector, of course, there would be patents and holds and all kinds of things on some of the basic research, and that's not where it should be held.

So, again, Dr. Collins, we owe you a great debt in being so forceful at that time and convincing us that this should remain in the public sector, because right now, because of this—a researcher anywhere in the world can get data from the Human Genome Project and further that research on.

To me, this again is a legacy that is almost incomparable in some ways. I think that the fact that we kept this in the public sector, again, is going to serve us well, not today but also in the future just making sure that everyone has access to it, and no one has to pay a single dime to get that information.

So, with that, again, Dr. Collins, thank you for your great service in that regard. I would yield now, to Senator Specter, of course, who just came back.

THE COST TO CURE CANCER

Senator SPECTER. Well, thank you, Mr. Chairman.

I've been dealing with you, Dr. Niederhuber on the cancer issue. President Nixon made his famous declaration in 1970 on a War Against Cancer, and I do believe that had that war been pursued with the same intensity as other wars, many of us wouldn't have contracted cancer.

We've asked for a projection as to what it would cost to "cure" cancer, and I put cure in quotation marks, because absolutes are understandably impossible, but were we to make a major frontal assault, and you come back with a figure of $335 billion over the next 15 years.

What are the realities as to how far we can go on attaining the goal of a cure? We know that there are many, many strains.

There's been an enormous amount of research, there's been an enormous amount of progress. Talking to Senator Lindsay Graham about his mother who had Hodgkin's years ago—very, very different world from the really complex regimen that I had—am having, really—on chemotherapy. So, what is the reality? How close could he have come to a "cure"?

Dr. NIEDERHUBER. Senator, you always ask the tough question.

First of all, I'd like to say a word of congratulations to you for finishing your 12th cycle of chemotherapy. I suspect no one in the room knows, perhaps, better than I do, how difficult it is to go through these cycles of chemotherapy.

So, you're to be congratulated.

Senator SPECTER. Thank you.

Dr. NIEDERHUBER. I talked to a friend of ours at the University of Pennsylvania just a couple of days ago, and he also lauds how you've been able to do this, and do it without missing a minute of work. So, you're to be congratulated.

Cancer is, as you mentioned, is many, many diseases. Maybe more than 1,000 diseases. As we get to understand the genetic differences—the genetic differences in breast cancer, the genetic differences in colon cancer—and how those genetic differences, as Dr. Zerhouni so eloquently pointed out, affect a network within the cell. How those cells interact—not just within the cancer, but how those cells interact with the so-called normal cells in which that cancer lives. It's a very complex, and very dynamic process.

I can't tell you how many years it will take to cure, or to make this disease much more of a chronic set of diseases that we can live with, that we can prevent—that's obviously our goal—that we can understand who's at risk from the genetic kinds of analysis that we can do on individuals, and can take measures.

Senator SPECTER. Well, how far will $335 billion take us over 15 years?

Dr. NIEDERHUBER. I think it will take us a long way.

Senator SPECTER. Because if you can quantify it, in some way, I think this subcommittee can take the lead in finding you the money, somehow.

Dr. NIEDERHUBER. What I did when I understood your asking that question and seeking advice from some of the communities, the cancer communities, the different organizations in the country, who also then came to me and asked for my opinion on this was to put together a team at NCI to think strategically about the various investments we're currently making, and what the opportunities for expanding those investments would be in the future.

We've, I think, prepared—or are in the process of preparing—what might be considered, I believe, a realistic, but well-thought out, and I would say, forward-looking business plan for the future. I'd be happy to——

Senator SPECTER. You've given us a timetable of 15 years, and you've given us a figure, $335 billion. I've only got 8 seconds left, although once the light goes on, you can still talk.

Senator HARKIN. Take more time.

Senator SPECTER. I haven't gotten to the question yet—where are we, how close to a cure?

Dr. NIEDERHUBER. I know it's a very difficult question and I'm not sure that I can give you a figure. We've felt that if we could add to the NCI budget $2 billion a year, each year for the next 5 years, that that would go a long way toward helping us build capacity within our country, in terms of attracting young people, attracting disciplines that haven't previously worked on cancer, to work on cancer.

I just attended a meeting that I sponsored, Monday and Tuesday, at which we brought together physicists, mathematicians, individuals who work on evolutionary biology—individuals who haven't worked in the field of cancer before. We had a 2-day meeting to brainstorm how these individuals might bring a different set of eyes, if you will, and a different set of thinking towards the magnitude of the problem that we face in cancer.

It was a very exciting meeting. I learned a lot from listening to those individuals, I think, that will greatly shape the future.

But, I think one of the things that came out of that meeting, Senator, was again what Dr. Collins said—that we, as a country, need to significantly invest in bringing bright, young people into the biological sciences, especially into cancer, and to create a capacity for us to be able to invest the resources of our country in this science. If we don't build that infrastructure and build that capacity, then it doesn't make any difference how much money we have. We have to have bright young people, we have to have people to work on the problem.

So, the first challenge, I think, for us at NCI is to increase our investment in attracting people to work on this particular problem.

I also think that we have a very real need to invest in retooling or re-engineering our clinical trial infrastructure. If we're going to take the steps forward that Dr. Collins has so eloquently talked about, and do drug discovery, and highly personalized characterization of each patient and their cancer, and match that with solutions of treatment, that's going to require different clinical trial structure than we currently have.

We worked, on July 1 and 2, with the National Institute of Medicine, at a 2-day symposium to talk about these issues about re-engineering the clinical trial structure. Again, that will take a significant amount of investment, financial investment, in order to retool that, re-engineer that, so that we can work effectively in the new era.

Senator SPECTER. Well, I won't ask another question, because others are waiting to question. But, when you talk about attracting the scientists, working with $335 billion, you can attract scientists. You talk about retooling clinical science, clinical tests, $335 billion will allow you to retool.

I know the questions are difficult, perhaps impossible, but we need to have, you know, the best professional judgment, because to sell that kind of money to the Congress is going to require something that we can put our hands around. When you get into the appropriations room, you have to have something more specific to pull out those big dollars.

Thank you, Mr. Chairman.

Senator HARKIN. Thank you, Senator Specter.

Senator Durbin.

NIH FUNDING AND SETTING PRIORITIES

Senator DURBIN. Thank you very much.

I want to just show a chart here, if I can, which is probably familiar to you, it may have been produced by some of you, and it shows the actual appropriations on the yellow bars, since fiscal year 2003 through fiscal year 2009 and the purchasing power at NIH that came from those appropriations.

It shows two things—first, that the amount that has been appropriated by Congress has not kept up with the inflation that you face, and so the actual amount available for medical research and all of your other endeavors has actually declined during these years.

The second point it makes is the administration and Congress made conscious decisions during this period of time to initiate a war that costs $15 billion a month, and to give tax cuts to the wealthiest people in America, so there were fewer dollars available for domestic discretionary spending, as a result of those two major policy decisions.

In that backdrop, I'd like to ask you to address one general question. I have a chart here—you're undoubtedly familiar with it, which shows the funding at each Institute at the National Institute of Health during this same period of time, and in fact, it goes back a little further in time, to 1998.

Until 2003, the amount of money to each one of the Institutes that you're in charge of was growing, and this was because of the commitment to double the medical research, and then comes that year—as evidenced on the other chart, it started to flatten out, and decline, and that shows the way that that's headed.

My question is fairly general—I started by saying that it's not uncommon for Members of the Senate to be visited by people from our States who have members of their family who are suffering from a disease—a wide spectrum of diseases. Without fail, they all ask us for more funding for medical research for the disease that affects someone they love.

They all argue that not enough money is going to that research, that field of research. I kind of took the position long ago—rightly or wrongly—I couldn't decide, I'm a liberal arts lawyer, what do I know about where the money ought to go? I said, I'm just going to give the NIH as much money as I can in the aggregate, and I hope they'll make the right decision.

It turns out that was a probably incorrect, if not simplistic answer. We do fund the Institutes. We really, kind of, decide at the congressional level, how much money will go to each Institute. There are winners and losers in that process.

So, when the family with a child—an autistic child—comes to see me, and says, "You're not spending enough money on autism. Don't you know, Senator, that 1 out of every 150 kids in America has this disorder?"

In my State, in the last 10 years, there's been a 353 percent increase in the diagnosis of autism, and of course, the costs are unimaginable for these children, and their care throughout their entire lives.

So, my first question—fairly simple question—but maybe not easy to answer. If we gave you $30 billion, and didn't have any strings attached, what would be the difference in this chart? Do we make choices—political choices—on Institutes, which you as researchers and doctors, step back from and say, "That isn't where I'd spend the money."

Dr. ZERHOUNI. This is a great question, this is a question I face all the time, personally. I know, over the past 5 years, I can tell you, there's no tears left in my lachrymal glands about how you make those decisions.

That's the important question, but it's not true that all of the money, when it doubled, went into the same things without any change or any decisions. Actually, if you look at the topics that NIH has, over a period of 10 years, for example, 50 percent of the efforts that we make in any one area, turn over in about 8 years.

GENOMICS

So, although NIH, you have a $30 billion budget, and you see these budgets, what's underneath these curves, is very different. For example, if you look at the efforts that are done in genomics, those didn't exist 10 years ago across all of the Institutes. Every single Institute here, I will tell you, spent 5, 10 percent of its dollars on these genomic studies, which were not done 10 years ago. Bio-computing—if you look at their basis—are available for biocomputing, for doing research on every disease—autism included, or any other diseases, these were not there 10 years ago.

We just developed, for example, through Roadmap, a Chemical Genomics Center. That center, that Dr. Francis Collins reflected about, can perform, in 2 days, 1.5 million tests. This is the equivalent of what it would have taken a scientific group to do in 15 years.

So, there are things that you change, the process that you have to really engage into is an open, transparent, portfolio analysis process, which we do.

Senator DURBIN. I'm running out of time. Maybe it will take you a moment, maybe you can't answer this. But, if we gave you $30 billion, with no strings attached, would this look the same?

Dr. ZERHOUNI. No, absolutely not. It never looks the same, from year to year—even between 2003 and today.

NIH FUNDING

Senator DURBIN. My point is, are we pushing allocating, politically, on our end of it, research into areas that you think are not the best expenditure of limited tax dollars?

Dr. ZERHOUNI. I would say that this is not an issue, in the aggregate. Frankly, Congress expresses priorities, we have an independent peer-review process which we absolutely cherish, because it is the process by which we go into scientific opportunity.

So, I think what is important, however, is that without the dollars, you tend to have to make choices that sustain what you have, and do not allow you to be as risk-taking as you would, otherwise.

DISEASE FUNDING

Senator DURBIN. Mr. Chairman, can I ask one last question?

Senator HARKIN. Sure.

Senator DURBIN. Would you address this issue of autism? I know there have been so many theories——

Dr. ZERHOUNI. Right.

Senator DURBIN. The parents that come see us share compelling stories about what they're dealing with, and arguing that we're not putting in the adequate money into research into this disease.

Dr. ZERHOUNI. Autism is one of the most important and greatest concerns that I have, as well as my colleagues, in particular, National Institute of Mental Health, Dr. Insel.

As you know, we have put an Inter-agency Committee on Autism, that is coming up with a strategic plan—that is how we're going to drive, essentially, the investments in autism, we're funding more centers; you just heard about a study that came out last week about the first really important discoveries in terms of the genetics of autism. I think it's advancing, it's progressing.

Could I use twice the money? Absolutely, I could. But I have other competing priorities, too.

Senator DURBIN. Thanks, Mr. Chairman.

Senator HARKIN. Thank you.

Senator Murray.

TRAUMATIC BRAIN INJURY

Senator MURRAY. Well, thank you very much, Mr. Chairman, and thank you for an excellent presentation. I really appreciate the tremendous work that all of you do.

You focused a lot on diseases—one of the, kind of the other side of the picture that I've been looking at as a member of the Veterans' Committee and working with returning soldiers on traumatic brain injuries and Post-Traumatic Stress Syndrome, and the growing number of men and women that are dealing with that, and the broader picture across America of neurological disease and disorders, and injuries and was surprised to learn that nearly 100 million Americans are affected by that, and the huge impact on people's health and our economy—I think it's $1 trillion that's being spent on neurological illnesses, the long-term impacts of that. Can you talk to me a little bit about what NIH is doing in a coordinated neurotechnology research, and what we can expect?

Dr. ZERHOUNI. In terms of traumatic brain injuries, we have really increased our investment—it's about $87 million a year now, as compared to a few million just a few years ago, primarily because of the issues—fundamental issues, related to our understanding of traumatic brain injury in the context of conflict, and the Iraq war, in particular.

In terms of injuries, generally, when you look at all sorts of injuries, we spend about $17 million, understanding musculo-scalpal injury, and all types of injuries. However, at this moment, this is not the only focus we have.

In collaboration with the Department of Defense, we have mounted an initiative in trying to understand both traumatic injury at the fundamental level, and Post-Traumatic Stress Disorder.

Now, when you really look at the impact of Post-Traumatic Stress Disorder and our understanding of it, you realize that this is going to require a response that is not just affecting the individual that is affected by PTSD, but the family around the individual, the community around the individual, and we do have to have a proactive response, because there are 1.7 million service members that have served in Iraq, and about 15 percent of those suffer from PTSD, a major public health issue, that will require full spectrum.

We do the research; we're collaborating with the Armed Services today on a $70 million joint project to create, in fact, the ability to diagnose PTSD very reliably. Then, with the Department of Defense, we're working on a project that will create community centers, so that we can, in fact, detect and manage that on the ground.

Senator MURRAY. So, we can expect to see a coordinated, solid look at this?

Dr. ZERHOUNI. Actually, you know, it's interesting—we have never been more coordinated than on this issue, across agencies, including DOD, VA, NIH, CDC, all of us.

PANCREATIC CANCER RESEARCH

Senator MURRAY. Fantastic. Thank you, I appreciate that.

On another question, Senator Durbin mentioned we have constituents who come to us—one of the groups that I'm hearing a lot from is the pancreatic cancer groups, they are very concerned. They know that NCI developed, I think it was 39 recommendations for pancreatic research back in 2001, and only 5 of those are being implemented. Can someone give me an update on where we are with pancreatic research? There's a growing trend of that.

Dr. NIEDERHUBER. Well, we're continuing to increase our incentives to the research community but trying to write specific RFA grant applications or opportunities. We continue to support, through the SPORE program, our Specialized Program of Research Excellence, which is focused on translational research.

So, I think we can continue to put resources on the table and ask for applications due to increased interest.

The second, and probably more stimulatory work is our whole genome scanning. We are actually looking at pancreas, in large cohorts, and one of the organ sites to try to determine, if we can, what regions in the genome might predict risk for developing pancreatic cancer.

Senator MURRAY. So, there's a lot of potential at that point?

Dr. NIEDERHUBER. So, there's a lot of potential to inform that. We hope, too, that the TCGA pilot project will eventually get expanded to other tumors—pancreas would certainly one of those that we'd be very, very interested in doing, as that pilot project is proving very successful.

HIV/AIDS VACCINE TRIALS NETWORK LIABILITY ISSUES

Senator MURRAY. Thank you very much, I appreciate that.

Dr. Fauci, while you're in front of me, as you well know, Fred Hutchinson Cancer Research Center in my home State is working with the NIH to administer the HIV/AIDS vaccine trials network, and it's inherently a Government function, they are doing the re-

search on it, and they're very concerned about being sued for damages, and the issue of liability is really threatening them. Can you tell me, is there any update on that?

Dr. FAUCI. We've been working very closely with the officials, at the Institute, at the University of Washington, particularly at the Fred Hutchinson Cancer Research Center (the Hutch), because as you know—and for those who are not aware of it—the data center for our vast vaccine trials network is centered at the Hutch, with Dr. Lawrence Corey being the principal investigator.

The issue is the concern that of, in fact, there is a suit against an adverse event that might occur somewhere far distant to the Hutch, what would that mean with regard to the liability and the vulnerability of the Institution for being funded? So, we're working very closely with the officials from the Hutch, together with members of the Department of Health and Human Services to figure out if we can evoke some of the existing authorities to help cover.

The idea of insurance itself—they have plenty of insurance there, but they're afraid that if it's a massive suit, that they would not be able to cover that. So, we really—literally—on a weekly and monthly basis, are trying to work something. I know officials have met with me, with people from Dr. Zerhouni's office, and himself, as well as with people at the Department of Health and Human Services, Secretary Levitt's staff—so we're actively on that. I do hope, and feel optimistic that we'll come to some sort of resolution, so that we can continue without the anxiety of liability.

Senator MURRAY. I really—this is really incredibly important research that they're doing, I would hate to see it halted or slowed down as a result of the liability issues.

Dr. FAUCI. We agree with you completely, Senator.

Senator MURRAY. Okay, thank you very much. I appreciate it.

Thank you, Mr. Chairman.

Senator HARKIN. Thank you, Senator Murray.

Senator Cochran.

OBESITY CHALLENGES

Senator COCHRAN. Mr. Chairman, thank you very much.

Dr. Nabel, I'm advised that since the early 1990s, the obesity rate has increased by 33 percent, resulting in serious health consequences for over 60 million people.

Ten years ago, there were guidelines that NIH issues, regarding overweight and obese challenges, and physicians have been relying on those guidelines for 10 years. Is it time that we updated the guidelines? Or does your Institute, or others, have specific plans to deal with the challenges that this problem presents?

Dr. NABEL. Senator Cochran, that's an excellent question and you importantly highlight the grave importance of overweight and obesity in our country, particularly among young people, and we're very, very concerned.

The answer is yes—we're in the process right now, the National Heart, Lung and Blood Institute—is in the process right now, in collaboration with our partners, the American Heart Association, and the American College of Cardiology, to update our obesity guidelines. We will have those available soon for adults, and impor-

tantly, for children, as well. A very important task is to get those guidelines implemented into clinical practice.

CARDIOVASCULAR GUIDELINES

Another task that we are—have embarked on, Senator Cochran—is to develop a set of integrated cardiovascular guidelines. In the past, we've had guidelines for blood pressure, for cholesterol, for obesity, and it's really time we begin to integrate those.

So, we started down that road, we're using a web-based tool, because we know most people, now, get their information through the Internet—we want this to be a consumer-driven project, again, in partnership with the Heart Association, the College of Cardiology.

We're hoping that this is a tool by which people can understand their composite risk for heart disease and obesity, given all of these individual risk factors.

So, the answer is yes, sir, we're working very hard at it.

Senator COCHRAN. I know one other area that you're familiar with is the Jackson Heart Study, based in Jackson, Mississippi, named for the city, to try to improve our screening and knowledge of heart disease and things that can be done—societal changes, diet, exercise, the like—to more successfully deal with that problem. What is the status of that project, and is there a continuing need for funding for this review that's being undertaken?

Dr. NABEL. Well, thank you very much, Senator. I want to personally thank you for the time and attention that you have brought to the Jackson Heart Study. You know that it's a very, very important project to us at the National Heart, Lung and Blood Institute, and we have worked collaboratively with you, and your office, as well as individuals at the University of Mississippi, Jackson State, and other institutions in Mississippi to bring this to fruition.

We have a lifetime commitment to this project. We believe that this project is so important, in terms of understanding the origins and the development and the treatment of heart disease in African-Americans in this country—it's critically important to us, as a Nation, and we will stay steadfastly committed to it.

ADDITIONAL FUNDING FOR NIH

Senator COCHRAN. Dr. Zerhouni, we're really pleased that the committee is moving to increase the appropriations for NIH, and I'm not going to make any predictions before we get through our work, but I think there is a consensus in this committee to do just that. What would an additional $1 billion increase do in terms of practical consequences at NIH in what you're able to accomplish?

Dr. ZERHOUNI. You said $1 billion?

Senator COCHRAN. Yes.

Dr. ZERHOUNI. Okay. If I had my choice, the first thing I would do, is I would really fund and protect the next generation of scientists. I would create a lock box within the budget, and say, we need to absolutely fund the next generation, and it has to be that number, and come hell or high water, we will fund them. So, the first thing is protect that future of protectors, who are going to follow these clues—if you don't have them, you don't have a research enterprise. That's number one.

The second is to address what I think are important resources across the entire Nation that are absolutely needed to conduct clinical trials, they are like what Dr. Niederhuber was talking about—to do, and you want to conduct research—we have to have the physical resources to do that, and to allow laboratory tests, to allow screening, for example, of millions of compounds, when we have a lead, or a target.

Dr. Collins was talking about the investment we made through the roadmap through chemical genomics. With the robotics technology that we've implemented at NIH, we can do 1.5 million tests in a day and a half. Well, you couldn't do that 5 years ago. That's what I would like to expand, so that more people have that availability.

The third investment that I would make is engage the community of scientists in more integrative science. Work across disciplines, fund them so that at the end of the day, they can coordinate their work to address problems that, as I said in my opening statement, tend to be very complex, and they require the collaboration of physicists, mathematicians, biologists, doctors and nurses, endopediologists—all of these need to be able to work together. It's not so easy to do when you don't have the dollars to sustain that infrastructure.

So, the third point—$1 billion won't be enough, actually, to do all this—is absolutely continue to encourage innovation—breakthrough innovation. Encourage people like the Pioneer Award, the New Innovator Awards, and we are launching a new program called Transformative RO1s—we are doing it, but it's just not enough. We absolutely need to tell people, "It is the best place to do research, America is the best place to do research, and we will actually give you the freedom to explore ideas that have been knocked out through, by all of us here today."

Those three things—young investigators, infrastructure to conduct better research with better resources at a faster pace, and give the leeway, the freedom for people to explore new avenues that we may not be exploring today.

Senator COCHRAN. Thank you very much, thank you for your leadership, all of you.

Dr. Collins, best wishes to you, as you move onto other interests and pursuits, thank you for your service.

PANDEMIC INFLUENZA VACCINE DEVELOPMENT

Senator HARKIN. Thank you, Dr. Zerhouni, for that last answer to that question, I thought that really laid it out, where we ought to be headed.

Dr. Fauci, let me pick up with you, here, on pandemic flu. It's sort of, you know, we've had hearings with you in the past on this, and talked about the threats of pandemic flu. It's sort of, somehow faded to the background, although things that I read about and keep up on indicate that the threat is still there, as real as it ever has been.

We've been trying to develop vaccines, and to—develop, I should say, develop systems for developing vaccines—that can respond to whatever the strain is that might be the outbreak.

Most of it's been egg-based in the past, we know that takes a long time, and then we went into cell-based, but that still takes a few months, several months, to develop the amount of vaccines that we need. I keep hearing about other kinds of ways of developing vaccines in a more rapid manner, I'm not—I can't speak about them, I don't know much about them, and so my question is, what's happening with—in your shop—in systems developments so, to respond to a pandemic flu outbreak? To get the vaccines made as rapidly as possible?

Dr. FAUCI. Well, thank you for that question. Just because Mr. Chairman, as you well know better than anybody—just because something is not on the front pages anymore, that doesn't mean that it's not an important issue.

So, there are two parts to your question that I can answer very briefly and succinctly. First, where do we stand with regard to a potential pandemic flu? That's not gotten a lot of press lately.

Number two, what about the investments that we spoke about at several committee hearings that you had, that I discussed with you at an official hearing and in private, about some of the systems involved, and some of our previous lack of ability to scale up manufacturing of vaccines, and surge, if, in fact, we have the unfortunate event of a transition from an endemic virus that still currently is in chickens. H5NI is still killing a lot of chickens, in Southeast Asia, and occasionally we see a burst of a transmission in a particular region, with culling of the chickens, and then it dies down.

The numbers now, we have about 385 human cases, 243 deaths as of yesterday, which gives you a sense of how the threat of the pandemic is emerging. That means it's smoldering, it has not gone away.

What have we done from a scientific standpoint? There have been major advances that I welcome the opportunity and thank you for asking the question about, with regard to some of the things that we set into play a year, 2, or 3 years ago. There's been a significant amount of movement now by several companies to varying proportions, away from egg-based, more towards cell-based, vaccine manufacturing which gives a considerable degree of flexibility, number one.

Number three, and I think to myself as a scientist, this is perhaps the most exciting—as I mentioned to you previously, about a year or so ago, there is great potential for the use of adjuvants. As you know, an adjuvant is a compound that you give together with the main component of a vaccine, that we call the immunogen, and it has the capability of doing two things.

It allows you to get an amplification of effect with a lesser dose; this is critical to stockpiling.

Number four, and we didn't know this for sure, but we've seen it in a number of other studies, is that it broadens the breadth of the response, which means, critically, that if we're looking at a vaccine that's circulating in Southeast Asia now, and we make a vaccine from that virus, there's always the possibility, if not the likelihood, that if it evolves to now become very efficient in going from human to human, if we stockpile that particular virus vaccine, we're going to have to change it—perhaps significantly—to keep up with the evolving strain.

What we have found out in three or four separate studies, conducted either by ourselves or together with pharmaceutical companies, or by pharmaceutical companies alone, is that the use of adjuvants has now dramatically increased our capability of scaling up.

So, what was formerly the famous 90 micrograms times two that I told you about several times, we can get down, now, to 7.5 micrograms, or 3.75 micrograms, times two.

And then, the final part of that is that much to our—I wouldn't say surprise, because I would like to have predicted—but much to our gratification, the response to a strain that's an Indonesian strain, when you vaccinate you get cross reactivity now, to some of the evolving strains. So, this really is very good news for the ability to scale up, and in fact, have a stockpile that would be more than just a stop-gap, but would actually, might afford this broader cross-protection.

So, again, though it hasn't been highly publicized, I think the news is all gradually heading in the right direction.

MOLECULAR ADVANCES IN VACCINE DEVELOPMENT

Senator HARKIN. Is there something besides cell-based developments that's going on?

Dr. FAUCI. There's the whole issue of the molecular-biological approach, because the standard vaccinology is, you get the virus itself, whether you grow it in eggs, or you grow it in cells, it's still the virus itself, and then you purify it, spin it down, get the right components of it. That's standard, classical vaccinology.

We're moving to what we call the 21st century vaccinology, which means you can, for example, take DNA, and insert into that the coding elements for a particular, specific protein, in this case with influenza, it would be the hemagglutinin, or the neuraminidase, or the M-Protein, and if successful, you can make an unlimited amount by the production using what we know from decades of experience with molecular biology, and recombinant DNA technology. We're starting to see that, right now, evolve and replace the standard vaccinology.

Dr. Zerhouni reminded me of a question that you didn't ask, but you've asked me in the past, is where we are with the universal vaccine, namely are we making headway in that? Some of the animal studies, again, are looking promising. This is one of those real tough nuts to crack, but I hope that at a future hearing, we'll be able to come to you with some real hard data that we've actually made progress in getting a product that could actually handle the drifting strains as they evolve from one year to another.

AIDS VACCINE RESEARCH

Senator HARKIN. To go from that kind of good news, and hopeful outlook, I now go to the AIDS vaccine.

Dr. FAUCI. Yes.

Senator HARKIN. All of the years and the money that's been spent on that, and the depressing news that we received recently, that not only is the AIDS vaccine not working, it may actually increase the susceptibility to AIDS. So, where are we? Where are we heading?

Dr. FAUCI. Well, where we're heading is a bit more back to the fundamental basics of asking and answering some of the questions that I mentioned to you and this committee years ago, related to the fact that HIV is really very different. In vaccinology, in general, when we make a vaccine, the standard paradigm is to make a vaccine that mimics natural infection. Because when all is said and done, when you're dealing with smallpox, when you're dealing with influenza, when you're dealing with polio, the body ultimately induces successfully an immune response, and although people get sick, and some die, at the end of the day, that virus, that microbe induces a response that completely eradicates the particular microbe from the body.

So, nature is smarter than we are, so when we want to make a vaccine, we want to mimic natural infection.

Senator HARKIN. Yeah, I understand.

Dr. FAUCI. The problem with HIV is that the body, to our great dismay, does not make an adequate immune response against the virus, such that there are essentially no examples of a person who gets infected, has an established infection, and then eliminate the virus from the body.

The reason is the way the virus presents itself: the body doesn't recognize it in the way that it induces a protective response. So, the failures that you've been hearing about, were that we were hoping that with the balance between empiricism, and fundamental scientific concept questions, we would be fortunate enough to have a situation where it would work.

It's becoming very, very clear now, that we need to go back and try and make ourselves smarter than the body, namely by developing whatever it is that—we call it an epitope, which is a component of the virus—and present it to the body in a way that would have it induce neutralizing antibodies that would ultimately protect.

So, you heard about the disappointing Merck study, it was called the STEP study, we were partners in that. And right now, we're going to very carefully go ahead and raise the bar a bit higher, before we go ahead into a big clinical trial, and turn the knob more towards asking and answering some of those fundamental questions.

We actually had a very successful summit in March of this past year, and we gathered all of the players, and even some people not involved in HIV vaccines, to plot the way over the next several years, and that's what we're trying to do.

CANCER AND THE IMMUNE SYSTEM

Senator HARKIN. Thank you very much.

Well, thank you very much, Dr. Fauci, for bringing us up on that.

I have a couple of things I wanted to bring up with Dr. Niederhuber on cancer research.

I wanted to get your thoughts on a researcher, you may not be familiar with, but I hope you will look into this. There's a researcher at Wake Forest that I met a few weeks ago and then have had some correspondence with—he recently presented a paper at UCLA that I heard about, his name is Jiang Cui, C-U-I, Dr. Jiang Cui.

He came to my attention because it was told to me that he'd been bringing mice with certain immune cells that were resistant to cancer. That no matter how much cancer cells were injected into the mice, the mice never got cancer.

Then he was taking some of these immune cells from these mice and putting them into other mice, and when he did that, those mice didn't get cancer. Well, this kind of intrigued me, so I met with him, he had quite an interesting laptop display that he showed me on this. These immune cells—he called them granulocytes, which I've never even heard of before.

Now, again, this is in mice—I understand mice are different than humans—but as someone once said, we're about 90 percent rat ourselves, close to that, anyway. It doesn't matter to just politicians, I mean all of us.

So it's very close. So, again, it raises the possibility that you can use the immune system cells to boost a cancer patient's resistance, an ability to fight the disease. Are you aware of his research at all? I asked him if he'd had an NIH grant, he said he did, once, some time ago, but he doesn't now. I just wondered if you were at all familiar with his research, at all, at Wake Forest. If not, that's fine. I just encourage you to take a look at it.

Dr. NIEDERHUBER. I'm a little bit familiar with it, Senator, he has had grants—two grants, I believe, in the past—an RO1, and then an R55 that was converted to an RO1. Both of those lapsed and he did not come back in for additional funding. Both of those were in areas that weren't quite related to what you're describing. He does have an IND which allows him to do research in this area, neither using these granulocytes that he harvests from patients nor in mouse models.

I would only say that I think that, as you're very much aware, we have probably at the NCI, and also with our colleagues at the NIAID, some of the best immunologists in the world, that are working not only on infectious disease and inflammation, but also on the relationship of cancer to the immune system.

I know that you are very familiar with the similar work in what we call cell-based therapy, of Steve Rosenberg. I think this is probably the most exciting work in the country, or maybe even in the world, right now, in terms of using cells from our immune system, tricking them or arming them in a way that they can specifically attack cancer.

So, we've very excited about the progress that Dr. Rosenberg has made. I think he is out in front as one of the real leaders in this—what I would call—cell-based therapy. There are certainly other workers across the country, some funded, some not funded, that are doing some similar things, but I don't think any of them at quite the sophistication of Dr. Rosenberg.

CONFLICT OF INTEREST IN EXTRAMURAL RESEARCH

Senator HARKIN. I'm obviously familiar with Dr. Rosenberg's history and what he's been doing, but it seems to me that that's the area that he's sort of been involved in for a long time, that is, the immune system and how that relates to our ability to fight off cancer cells. I thought of that when I met Dr. Cui, I thought of Dr. Rosenberg and all the work that he'd done in the past on this.

But, I would appreciate it if you'd take a look at that and see if there's anything different there, that what Dr. Cui is doing at Wake Forest.

[The information follows:]

DEPARTMENT OF HEALTH AND HUMAN SERVICES,
NATIONAL INSTITUTES OF HEALTH, NATIONAL CANCER INSTITUTE
BETHESDA, MARYLAND, *August 11, 2008.*

The Honorable TOM HARKIN,
United States Senate, Washington, DC.

DEAR SENATOR HARKIN: At the, July 16 hearing to consider Appropriations for the National Institutes of Health (NIH), you asked me to look into research done by Dr. Zheng Cui at Wake Forest University. Several scientists at the National Cancer Institute (NCI) have had the opportunity to examine Dr. Cui's work which is indeed very interesting. In the course of routine experimentation, Dr. Cui discovered a single male mouse that did not develop cancer despite repeated infusions with increasing numbers of cancer cells known to cause cancer in other mice. When he bred this mouse, he found that 40 percent of its progeny also proved resistant to cancer suggesting that there was an inherited genetic element to the observed resistance. Further experimentation has demonstrated that the immunity displayed in these mice is mediated by cellular elements of the immune system, called, as indicated at the hearing, granulocytes. The cellular immunity has proven to be effective against multiple types of cancer and has proved transferable. Injection of previously susceptible mice with granulocytes from resistant mice has conferred cancer resistance to the recipients. If the recipients already had cancer, the tumors regressed. Dr. Cui has not however been able to isolate the genes in the resistant mice responsible for this characteristic, postulating that this may be due to the fact that they are mobile genetic elements, genes that do not have a fixed location on a chromosome.

It is unclear what experiments were done with human granulocytes to determine that they too displayed the cancer resistance found in the mice. Perhaps an in vitro assay of the ability of these immune cells to kill a variety cancer cells would be informative. While in vitro experiments might be encouraging, there is not yet reason to believe that granulocyte infusion from a donor would have in vivo anti-tumor activity and no evidence to suggest that the infused granulocytes will traffic to tumor sites. An additional concern is the potential risk of graft versus host disease which is not a concern in the experimental mice, but would certainly be in humans. Dr. Cui's planned trial will attempt to determine the risk of this complication in which donor cells (lymphocytes) attack healthy cells in the recipient, leading to serious health problems. While the trial design only calls for the infusion of granulocytes, there is no guarantee that all lymphocyte contamination would be removed.

This approach differs somewhat from that of Dr. Steve Rosenberg. In Dr. Rosenberg's case, the transferred cells are lymphocytes which have been proven to have anti-tumor activity in vivo. In addition, Dr. Rosenberg's research now involves the use of the patient's own cells in the treatment of cancer rather than donor cells. The patient's cells are genetically modified outside of the body in order to increase their anti-tumor activity and are then infused back into the patient.

Dr. Cui's approach, while interesting does make certain leaps of faith with regard to the similarities between the mouse and the human. The upcoming clinical trial will determine whether these leaps were warranted. I appreciate your interest in cancer research and am pleased to have the opportunity to provide this information to you.

Sincerely,

JOHN E. NIEDERHUBER, M.D.,
Director, National Cancer Institute.

Senator HARKIN. I just have one other area that I really wanted to cover here, Dr. Zerhouni, conflict of interest. You led the way on changing the rules for NIH employees. I know you share my concerns about conflicts of interest among extramural investigators, as well. We have to maintain the public's trust in NIH, and eliminating conflict of interest is an important part of that.

I know you supported the amendment I offered in last month's Appropriations Committee markup to require HHS to issue "an advanced notice of proposed rulemaking," which will start the formal process of revising the current HHS guidelines.

Clearly, NIH and academic institutions will have to work together to end the problems that we've been reading about. There's obviously been some correspondence from other Senators in this regard and some of this has made its way into the press.

The HHS Inspector General recently found several problems with the way NIH is currently overseeing grantee institutions. For example, NIH couldn't provide an accurate count of the number of conflict of interest reports it had received. More importantly, the AIG found many Institutes basically take grantee institutions at their word, that they're following the regulations, rather than doing any oversight of their own.

Again, in your opinion, what should NIH be doing to improve its oversight of the extramural research that's being done, and any problems of conflict of interest in that extramural activity?

Dr. ZERHOUNI. As you know, the issue of conflict of interest has sort of grown in importance over the past 15 years, much more so than ever in our history, simply because of the intertwining of industry and academia, in terms of marketing and understanding the proper use of drugs.

We also need to state that there is good value to good interactions that are well-managed, between industry, academia, and Government that create public good. Many of the discoveries and the products that we make, come from that interaction.

So, the real challenge, Senator, is how do you balance, the good—the public good—that comes in from proper, fully disclosed, fully understood interactions that do not—do not—present a risk to either individuals, human subjects, or the risk to the objectivity of the science?

So, we need to work together, NIH, the institutions, Congress, to find exactly how this needs to be put in place. Given the fact that the world has changed, and given the fact that I think our number one priority is to make sure that the American public who funds this research is ensured that we have systems in place, common standards in place, that are transparent that allow us to also stratify the risk.

I don't believe there is the same degree of risk in terms of conflict of interest when you're talking about very early discovery or genetic research that doesn't have a human application, as opposed to a clinical trial. As opposed to teaching, giving opinions that are not evidence-based, or using scientific prestige to promote private interests.

That gradient, if you will, that stratification, needs to occur. So, what I'm hoping for is that, and something I've said all along, is that we need to come up with a consensus about common standards that all institutions need to use. If you really look at the Inspector General report, our own analysis, you'll find that institutions have not yet converged towards one common, coherent set that we can all implement, that's number one.

Number two, I think it's important to stratify the risk. I think it's different when you're talking about risking the life of someone, or imposing treatments that are not evidence-based on thousands of individuals, as opposed to doing good research that may discover the next cure for a disease.

I think we need to understand that better, and I think the advanced notice of rulemaking will establish that debate, so that we understand that.

Third, I believe that there is a cultural responsibility that is absolutely necessary for that. The first thing that has to happen is sunshine. So, I think I support the concept of sunshine in disclosing these relationships, first and foremost.

The second step after sunshine, is to understand how you manage those things to, guarantee the integrity of the process. You can't do that, really, in my opinion, without some third party that will be the arbiter of this between institutions and the NIH.

So, we need to think about some independent way of really being proactive, if you will, a sort of quality control over the process. It's really hard for NIH to, essentially, check 300,000 scientists out there, We don't have to rely on some degree of self-regulation, self-reporting, and I think that is the challenge that we all face.

We all want the same thing, which is let's not discourage innovation, but not at the expense of either individuals, or the integrity of the scientific process.

AAMC AND AAU RECOMMENDATIONS

Senator HARKIN. I'm assuming, Dr. Zerhouni, you would support the AAMC and the AAU recommendation that investigators should have to report all of their financial interests? Regardless of the amount, regardless of whether it might appear to be affected by their research? That's the idea of just sunshine, are you supporting that?

Dr. ZERHOUNI. I think so. I think we need to do that and actually when we looked at the issue at the NIH, one of the problems was lack of disclosure. I mean, you can't manage something you don't know about, right? I mean, how do you start managing something when there is no disclosure requirement? I think that's the number one step.

I think we also need to be very careful not to go too far and damage innovation by having very strict rules that are one-size-fits-all. I'd be willing to be very, very strict when it comes to risk to patients, risk to populations, and risk to the integrity of science. That's different than someone who has a patent, a discovery, a new device or a brilliant idea—I don't think we want to stub that, so reaching the balance is the key concept here, while preserving public trust.

FOOD ALLERGY RESEARCH

Senator HARKIN. I keep shifting back and forth, but I forgot to ask Dr. Fauci another question.

In my other capacity as Chairman of the Agriculture Committee, which has to do with a lot of food programs, and feeding programs, next year we have the reauthorization of the Child Nutrition bill, which provides funds for school lunch programs, school breakfast programs. Through all of this, I think maybe we've talked about this in the past, and I'm sure I've asking you about this at other hearings—the seemingly explosion of food allergies among kids.

Dr. FAUCI. Right.

Senator HARKIN. I'm hearing back from school that are having problems, because of all of the food allergies that kids have. So, what's happening out there, and what's your Institute doing to look at this, seemingly, explosion of food allergies?

Dr. FAUCI. Yes, that's a very, very important issue, in fact, you recall we had a hearing just on this particular subject. A lot is happening now, I think that there really is a full realization that this a serious problem. As you know, 6 to 8 percent of children less than 4 years old have a food allergy, and 4 percent of adults have a food allergy. There are 30,000 anaphylactic reactions a year, and about 150 to 250 deaths.

So, we really need to, actually—and this is what I believe we're on the way to being more successful than we were in the past—of rejuvenating the field along the lines that Dr. Zerhouni and Dr. Collins and everyone was talking about about getting people in the field who are interested, who are motivated to get involved, bring some of the more sophisticated science to try and understand what is the pathophysiological mechanism of why this is occurring, asking whether some of the old assumptions that we have about food allergies, including things like peanut allergy should we be exposing early or avoiding? Things like that.

Senator HARKIN. Which I asked you about at that hearing, remember? I mentioned to you——

Dr. FAUCI. Exactly, exactly.

Senator HARKIN. That, why China—they eat all those peanuts in China, and they don't have allergies?

Dr. FAUCI. Exactly—they boil them, we roast them.

Senator HARKIN. There's something going on.

Dr. FAUCI. In Israel, they give infants and children peanuts as a little snack, we don't.

So, there are so many fundamental questions and I'm so pleased, we had a hearing with Senator Dodd a few months ago, about what's going on in food allergy, and we're very pleased that we have a program of a new investigators. We are trying to ask some fundamental concept questions, hoping to bring new people into the field. We have committed about $5 million over 2 years and we're just now in the process of awarding those grants. To my great satisfaction, I think 11 out of 12, or maybe even 12 out of 12 of the investigators are actually people new to the field. That's very important when you think in terms of the things that Dr. Zerhouni said, about getting new, fresh, young ideas.

So, we have—in a very limited budget, I have to say—we've increased our food allergy allocations from a pittance of just less than $2 million to close to $13 million, but we really need to do much more, but in an arena of fiscal constraint, it's very difficult to do. So, we're really trying to jumpstart that system. But, I'm very pleased that you, and Senator Dodd, have brought that up, because it is now really focusing on the importance of the problem.

Dr. ZERHOUNI. If I may, Senator, also as part of the National Children's Study, there is a component of the Children's Study that is going to look carefully at this from the moment of conception, all the way to 21 years of age, trying to capture, in fact, the food exposures, if you will, that we have and the emergence of allergy, trying to understand a little bit better what happens in early life. Dr.

Dwayne Alexander is not here, but I'm sure he would have mentioned that and I think we've updated your office on that.

HEART ATTACK PREVENTION

Senator HARKIN. I'm going to reassure you that we are going to continue to fund the Children's Study. We're not going to let that one drop, either. We're going to continue to fund that.

I was, Dr. Nabel, I haven't asked you a question and I wanted to get to one thing. Since Tim Russert's death, we get a lot of people asking about, what are we doing to really prevent heart attacks? It seems like kind of random, and they happen, I'm just getting a lot of input into my office about that, they're going to their doctors, are they a risk for heart attack—what kind of research is being done in preventing heart attacks?

Dr. NABEL. Well, that's a very important and delicate question. Mr. Russert's death was a great tragic loss for our country and many of us have mourned his death.

We have now referred to this as the Russert Effect, you've probably seen stories in the newspaper, on television, of middle-aged men—a story in the Times a week ago, a middle-aged man, age 50, on a bike ride on a Saturday morning, didn't feel well, a little fatigued, a little short of breath, his partners had to leave him behind. He called his wife, ''I'm not well,'' he went home, laid down, and thought, ''Tim Russert.'' He drove himself to the hospital and he was having a heart attack.

It is true that we know a lot about the risk factors for heart disease and we're doing all we can to help individuals identify their risks very early in life and modify those risks.

Yet, at the end of the day, despite all of our best abilities to modify those risks, we know that at some time, a little bit of the blockage in the heart artery can break off, and that blockage might only be a 5 or a 10 percent blockage, might break off, leading to a blood clot and a heart attack.

That doesn't stop us from doing everything we can to help individuals understand their risk, and to help them to do all they can to modify their risk. As you know, we've had a very active program over the past 5 years for women and heart disease to have women identify the risk.

I think, quite honestly in all of our efforts to focus on women, we've left the men behind. Now we need to catch up, and help men remember that they're at great risk, as well.

It's really a public education, it's a campaign that we work on arduously, every day, with our partners, the American Heart Association, to help people understand their risk, and to take action.

STATINS AND MORTALITY

Senator HARKIN. Is there any evidence, at all, any medical evidence at all that the use of statins has reduced mortality—

Dr. NABEL. We know that the use of statins lowers your risk for having a heart event—by that I mean, a heart attack, or dying of a heart attack.

Senator HARKIN. Because I've been informed that there really is no medical evidence that statins has reduced either morbidity or mortality from heart attacks.

Dr. NABEL. For people who have known heart disease, the answer is yes, statins clearly reduce the risk for having a second heart attack, or for dying from heart disease.

Senator HARKIN. Which raises the question, should so many people be taking statins, who have never had any incidents of heart disease at all?

Dr. NABEL. That's exactly the question that needs to be asked, and that's the study that we would love to do. If we had incremental money in our budget.

Senator HARKIN. But we're spending billions of dollars a year taking statins——

Dr. NABEL. We are.

Senator HARKIN. There's a lot of counter-evidence that they really—unless you've had an incident——

Dr. NABEL. Yes.

Senator HARKIN. That it really doesn't prevent.

Dr. NABEL. You're right, Senator. What we're really doing, is we're hedging our bet. Because what we don't know, is that for individuals who are at low, or even moderate, risk for heart disease, does starting taking a statin—age 20, age 30, age 40, age 50, or even in childhood—make a difference? We don't know the answer to that question.

We know that if you're at a very high risk for heart disease, then you've got very high LDL cholesterol, and you've got two, three, four other risk factors, then yes, in that group, taking a statin does help.

But, the majority of people really taking statins in our country today are people who are hedging their bets. A little bit of an increase in blood pressure, a little bit of an increase in cholesterol, figure lowering your statin may be helpful. It's common judgment, it may be helpful, but we don't know the answer.

The study that we would like to do, is a longitudinal study of primary prevention. Does taking a statin when you start, say, in your 30s or 40s, when you might have one or two risk factors for heart disease, does that lower your risk, or prevent you from getting a heart attack in your 50s, 60s or 70s, or dying from heart disease? We would love to do that study, if we had the money.

Senator HARKIN. Why don't you do that study?

Dr. NABEL. We would love to, it's an expensive study.

Senator HARKIN. Well, tell me how much.

Dr. NABEL. We're estimating that——

Senator HARKIN. I mean, if not today, I mean, at least——

Dr. NABEL. Yes, it's in the estimate of hundreds of millions of dollars. Because you would need to enroll people very early in life, you would need to follow them carefully over decades—we could certainly do that study. We've done an equivalent in the Framingham Heart Study, we're doing it in the Jackson Heart Study.

But, at this point, to dedicate that size of sum of money from our budget, which is limited, it's just tough to do.

CARDIOVASCULAR DISEASE

Dr. ZERHOUNI. If I may, from the overall standpoint, not looking specifically at this—if you look at the total mortality and morbidity for cardiovascular disease and stroke, it has dropped by 60, 70 per-

cent. The real question is how do you and what do you attribute that drop to? Is it cessation of smoking? Is it taking aspirin? Is it taking, having good diets? There's controlling blood pressure, taking statins.

So, when you look at the policy aspect of this, how do you really start demonstrating whether or not something works or doesn't work? Well, you have to take the high-risk group. In this case, in statins, it's clear that if you take patients who have had a heart attack, therefore, absolute proof-positive that they have an underlying cardiovascular disease, the evidence is clear that statins do help reduce the number of second events, and so on.

The same thing is true when you're looking at the issue of secondary prevention, versus primary prevention, which is the topic that Dr. Nabel talks about. As a country, we're going to have to make that decision, why? Because there are many things we do, for example, in diabetes. Diabetes, we have oral drugs that reduce glycemia. We have, also, studies that NIDDK has done that show that if you use them as a pre-diabetic patient, when you're not diabetic, you will reduce the risk of the disease emerging.

What is the key to all of this? The key, Senator, is can we predict in the millions of people who take statins, those who have a real risk, as opposed to those who do not have a real risk? That's where the predictive nature of the genomic research and the personalized medicine research that Dr. Francis Collins has been talking about comes in. As long as we don't have that knowledge, you know we will have to do very long trials where we follow people over many years, which are very costly.

BIOLOGY OF AGING AND THE AGING PROCESS

Senator HARKIN. Speaking of long years, Dr. Zerhouni, I want to talk about the biology of aging. Diseases like Alzheimer's, you mentioned diabetes, heart failure, stroke—operate in different ways, but the one thing that they all have in common, they tend to strike older people.

Traditionally, our research in these diseases has approached them separately, one at a time, we look at these diseases, and we investigate them. Now, we're learning more about the basic biology of aging, that suggests there may be ways to postpone all of these diseases, by slowing down the human aging process.

If we could add 5 to 7 years of healthy, vital life to millions of people, it would have an enormous impact on healthcare spending. Plus, the fact that we know that most of the spending on medical care in this country goes in the last couple of years of life.

Someone once said to me, a long time ago, that one of the primary goals of biomedical research was to enable to die young, as late in life as possible. I've always remembered that. So, what are you doing, what are you looking at in terms of this whole biology of aging and the aging process, as it might impact all of these different—heart diseases, strokes, diabetes, and everything else?

Dr. ZERHOUNI. Right.

Senator HARKIN. I imagine that must spill over into Dr. Collins' area, too, big-time.

Dr. ZERHOUNI. I will start and then he'll tell you what the future is like.

Clearly, when you look at the aging process, and you started by saying, there are multiple conditions that affect people at the same time.

Senator HARKIN. Yes.

Dr. ZERHOUNI. So, there are really two questions, there are—do we age the same way? Does our population age in the same way, or do we have clusters? People age one way and then others age another way?

So, the first thing is, is there a heterogeneity in aging, do we all age in the same fashion? We know, today, that the aging process over the past 30, 40 years—people are living longer and healthier, so the disability rates for seniors have dropped. So, we know that there are things you can do that seem to improve your aging process.

Second, we also know, as Dr. Nabel was just mentioning, and she's saying something very important—we've done one disease at a time, now we need to integrate the factors, and it's very clear that if you look at the aging process, some of us age faster, and seem to present a collated set of diseases—diabetes, high blood pressure, the metabolic sort of—low exercise levels, obesity, Alzheimer's disease that relates, now, as we know, to diabetes in some ways, and cardiovascular disease. You look at the genetic spectrum of these diseases, one subgroup seems to be affected more than other subgroups, and we are honing down on those discoveries.

So, that's one aspect of the aging process. Are we accelerating unhealthy aging in certain members of our population, what is the evidence that that's the case, and what can we do about it? So, that's one way to approach the problem, Senator.

The second problem is we also have evidence that you can, in fact, slow down the aging process. So, we have found a molecule—there's a famous molecule now, retro, which comes from red wine, which seems to be, in fact, having this effect.

The other remarkable finding is that if you have caloric restrictions—if you just reduce the number of calories in an experiment in animals, you can lengthen life expectancy by 30, 40 percent.

Our researchers at the NIA are doing another experiment where they're saying, what if you have one day of fasting and another day where you don't fast? So, intermittent fasting? They see the same results, even without loss of weight.

So, there's fundamental research on one end that shows that there are mechanisms that complex network of molecules that say, there is a way of good, graceful, healthy aging. There's also this body of research that shows that, in fact, chronic diseases seem to start in a combinatorial way where you seem to have everything at once and then you have to take 12 drugs to live your life and those are not the exact same processes.

Well, now I'll turn it over to Francis, who's done a lot of work with NIA about how do we, then, see the future in these two directions?

GENETICS OF AGING

Dr. COLLINS. So, despite all of the exciting research that's going on, I think you're right, Senator, that the goal ought to be to try to give each of us the chance to die young, but at a very old age.

The death rate will probably continue to be one per person, at least that's my prediction in the current climate.

But I'd like to see that death rate extended out, to a full four score and ten or more for all of us.

So, how are we going to get there? Obviously a great area of interest is what is the program that's basically built into our system that is supposed to be responsible for the fact that we don't live forever? In evolutionary terms, there needs to be such a program, otherwise, nothing could ever really progress, so lifespan has to be limited so future generations can have the resources, and let the older generations fade away.

But, obviously, we've learned a lot about the way in which different individuals seem to age at different rates, simply by observing them—what's going on there?

There are studies now underway looking specifically at individuals who have reached the age of 100 or more, to ask the question, do they have some genetic susceptibility to very long lives? This is not a susceptibility to disease, this is the opposite side of that, the flip side of the coin.

In fact, there are, in the last couple of months, discoveries of exactly those kinds of genetic factors—based on the same strategy that Dr. Zerhouni talked about in his opening statement, that led to all of those banners on the chromosomes for various diseases—there are also genes that are good for you, apparently, and that are capable of giving you this kind of opportunity to live a long and healthy life.

If we understood how those worked a little bit better, then perhaps by modifying diet, lifestyle, we would contribute those same opportunities to people who don't have the inheritance—the genetic endowment—that they wish they did.

Another area that's of great interest, is studying nature's surprise experiments of individuals who have a very rapid aging process. Dr. Nabel and I, in our own research laboratories, are working on a disease called progeria, which is the most dramatic form of premature aging. These kids appear normal at birth, but by about a year of age, they stop growing, and then their hair falls out and their skin gets old and leathery, and they die, generally, at age 12 or 13, of a heart attack or a stroke. So, they're aging at about 7 times the normal rate.

My laboratory identified the genetic glitch in progeria 5 years ago, and it turns out to be in a gene that codes for a protein that had some fair amount of cell biology work already done on it. In just 5 years, we have gone from a complete enigma of what this rare disease was all about, to a clinical trial of a drug which appears to work quite well in an animal model. This trial being conducted in Boston, and now already a year along, with about 30 kids with this rare disease being treated.

That is breathtakingly quick, and it, again, is a testimonial to the richness of the research environment that's being created by NIH investments.

Is that disease anything like normal aging? Well, obviously it's dramatically accelerated, but we have now very strong evidence that that same pathway is just a little bit tweaked as we get older,

and maybe part of the time clock that we're all living with, hearing that ticking in the background, coming from this same pathway.

Therefore, studying the rare disease may teach us something about the common, universal feature of aging, which is a very exciting series of observations we can expect to make in the next few years.

Senator HARKIN. Well, that's very provocative.

Dr. COLLINS. Indeed.

Senator HARKIN. In a good way.

Dr. COLLINS. Yes.

PROMISE OF PERSONALIZED MEDICINE

Senator HARKIN. Is there anything anybody else wanted to bring up here, that wasn't probed, or asked or anything? Any of you want to make any other—Dr. Collins?

Dr. COLLINS. If I could, again, because it's my last chance, I think it has been mentioned by Dr. Zerhouni and others about personalized medicine, and I just wanted to say a word about that, in terms of the promise that this provides for where we may be able to go, in terms of clinical care.

We are learning, as you saw in the course of the last couple of hours, a remarkable amount about hereditary risk factors for disease. We've known they were there, we largely guessed at them by family history, everybody has a family history of something, and generally that gives us a clue about our own risks, and it's been the best clue we've had.

HERDITARY RISK FACTORS

But, we're unraveling—especially in the last 2 years—the molecular basis of those hereditary factors, at a prodigious pace. It's no accident that Science Magazine called this The Breakthrough of the Year in 2007, in all of science was this understanding of human heredity and how it plays a role in common disease.

That really does position us, relatively soon, to be able to offer to anybody who wants the information, a chance to find out, in a much more precise way, what their risk factors are—while they're still healthy—and then to design a plan of prevention that is the one-size-fits-all approach, not anymore it's focused on what that person most needs to pay attention to. That's pre-emptive, that's personalized, it's all of the things that Dr. Zerhouni is talking about in terms of where we need to go. It focuses on prevention, and spending our healthcare dollars keeping people well, instead of waiting until they're in the ICU for something that we might have been able to prevent.

PHARMACOGENOMICS

On top of that, we're learning a prodigious amount about the way in which drug responses also vary from person to person, allowing us—in the not too distant future—to do a more evidence-based assessment of which drug should that person get, and at what dose.

Senator Specter, who courageously is going through this experience with Hodgkin's disease—if we had just a bit more information, and we desperately need to get that—to pick exactly the right kind

of combination of chemotherapies for his particular situation, as opposed to a larger group of people, we could have an even better shot at reducing the likelihood of side effects, and improving the outcome, and we need to really push on that. But we're getting there at a pretty fast rate.

THERAPEUTIC TARGETS

Then, the therapeutics that we have to offer which, in many ways, we have been sticking with drugs that work pretty well, for decades, but we've really needed this breakthrough in an idea about new targets—that's what the genome has given us. For most of the pharmaceutical industry's history, they've been limited, pretty much, to working with 500 or 600 targets—the things that we knew something about. The human genome breaks that wide open, and all of these discoveries about genes for common disease are pointing us much more precisely towards targets that are not secondary in the problem, they're the primary place that you would want to go to apply your therapeutics.

We can see that happening for common diseases, and the drug industry is jumping on that appropriately, and for rare diseases, NIH has the chance to step in, and for neglected diseases of the developing world, as well, as we've recently seen done for some of those diseases like schistosomiasis.

So, I think, when we put that all together, we have a pretty exciting shift in the paradigm from waiting until illness strikes and hoping you have something to do for it, to focusing on prevention in an individualized way—which I think will motivate people a lot more to actually act on the prevention opportunities, because it's about them—it's not some sort of generic prescription—and the opportunity to change our therapeutic agenda in a direction that's much more rational and evidence based.

But we can't get there without the support of this wonderful Congress, and this subcommittee that you've so ably led. I think we all come here today in hopes that the difficult times of the last few years may be about to turn a corner, and that we can bring back into the fold, investigators who are on the edge of departing, and not returning. That's our hope. We don't want to see all of this done in Singapore. It would be great if a lot of it got done right here in the United States of America.

Senator HARKIN. Your remarks remind me, number one, that's why it is so important to pass the Genetic Information Nondiscrimination Act.

Dr. COLLINS. Absolutely.

INDIVIDUAL GENOME MAPPING

Senator HARKIN. Second, are we going to be able to afford—where do we get the price of mapping each of our own genes, like Dr. Watson did, and others, I mean, now what is it—$100,000 or something, and they wanted to get it down to just a few hundred dollars per person, is that really going to happen?

Dr. COLLINS. Oh, absolutely. We are on that pathway at a remarkable rate. In the last 2 years, two very new strategies for doing DNA sequencing have found there way, really, into the mainstream of this research arena, and one can now sequence a ge-

nome—which originally cost us, as you reported, somewhere in the neighborhood of $300 million for that first one. It can now be done for about $100,000, and the trajectory we're on, I would predict, will get us to the $1,000 genome in the next 6 or 7 years.

Already, now, one can—if you don't want the whole sequence, if you want to focus on, say, 1 million places in your genome where we know there are variations that might play a role in disease—you can do that, now, for about $1,000, in fact, there are companies out there that are marketing that directly to the public, which is an exciting thing, although some of us are a little worried about whether we're jumping the gun, here, in terms of knowing exactly what people should do with that information, but it's coming very fast.

The technology, the cost, are not going to be rate-limiting, what's going to be rate-limiting is to do the research to know what to do with that information so that people, once they have it, can be given good recommendations about how to reduce that risk and stay healthy, and that's a huge agenda for NIH right now, but those are—as you've heard—expensive, longer-term clinical studies—we should be doing them now, and not putting that off.

Senator HARKIN. I'm hopeful that sometime in the near future that we're going to find some—a dedicated source of revenue for NIH. I've got some thoughts on that, in fact, Senator Mark Hatfield and I had proposed that back in 1994.

Dr. COLLINS. I just remembered that, Senator.

Senator HARKIN. 1994 we proposed that, of course everything came crashing down, but maybe we'll revive that again, to get a dedicated source of revenue.

Well, it was very simple. It was everyone's health insurance policy would take a certain—and it was only just a few pennies, it wasn't very much—that would go for basic medial research to enhance prevention.

Well, I have never given up on that.

But, Dr. Zerhouni?

DR. ZERHOUNI'S FAREWELL REMARKS

Dr. ZERHOUNI. I'd like to just say two things—one is, 1,000 years from now, when people look back at 2007–2008, one of the things they'll remember is the impact of the human genome on the history of mankind. When $1,000 genome, or $100 genome—whatever it is—people will remember that as a defining event of the first decade of the 21st century.

The second is that, as they look back and they wonder about where were the Seven Wonders of the World then? As we do today with the pyramids and Taj Mahal, and I would say that they will remember that of the seven most wonderful institutions of that time, NIH was part of it.

As part that, I have a great privilege to have been, to be the Director of NIH, and to have been working with great colleagues.

So, I'd like to add my voice to both the appreciation we have for you, and for the members of the subcommittee and for your continuous understanding and support, and I'd like to take this opportunity to also add my voice and those of my colleagues at NIH to really wish Dr. Collins the greatest possible future. He's been an

enormous asset to our country, and to NIH, and I don't know if protocol allows, but I think we owe him a round of applause.

Senator HARKIN. Well, I join with you, Dr. Zerhouni.

Dr. Collins, you know the high esteem that I personally have for you, and I know that all of the members of the subcommittee—I know I can speak for my great friend Arlen Specter, too—we have the highest esteem for you. We thank you for all of your dedication to health, to research, and to the goals of research, which is to help us live healthier lives.

So, we wish you the best in whatever endeavors you're going to pursue and don't get too far away, we're going to need to call on you every once in a while, you know, to tell me things which I might understand 5 percent of, okay?

Dr. COLLINS. Call me anytime.

Senator HARKIN. I appreciate that.

Well, thank you all, very much.

Dr. Zerhouni, thank you for your great leadership, Dr. Fauci, Dr. Nabel, Dr. Niederhuber, all of you. Through you, to all of the other Institutes. Like I said, only because of time, and I had a farm bill that I had to get through this year that just kept going on and on and on and on, and other things, and we just weren't able to have the kind of hearings that I like to have with NIH.

But, I can assure you that—even if I'm not chairman next year Senator Specter will allow me to do that next year. We're going to have more at-length hearings with all of the Institutes next year.

But, again, thank you all very much for being here, thank you all for your great leadership in so many areas. We appreciate it.

ADDITIONAL COMMITTEE QUESTION

There will be additional questions that will be submitted for your response in the record.

[The following questions were not asked at the hearing, but was submitted to the Department for response subsequent to the hearing:]

QUESTIONS SUBMITTED BY SENATOR TOM HARKIN

K30 AWARDS

Question. Dr. Zerhouni, thank you for your continued leadership in supporting the transformation of clinical research and clinical research training through the establishment of the Clinical and Translational Science Awards (CTSA) initiative. As the NIH transitions to the CTSA program, there is the potential for an institution which has not yet been awarded a CTSA grant to also have its K30 Clinical Research Curriculum Award phased out. Because not every K30 award recipient institution will receive a CTSA grant, it seems to make sense to continue the K30 mechanism for those institutions which have not received a CTSA grant. Does the NIH and the NCRR have a plan for the continuation of K30 awards to those institutions not receiving a CTSA grant?

Answer. The K30 program supports curriculum development and has proven to be an extremely effective career development activity. The program was initiated in fiscal year 1999 following recommendations from an NIH panel on clinical research and expanded to 43 awards in fiscal year 2000. The program was re-competed in fiscal year 2005, when the average grant cost was increased from $200,000 to $300,000, and 51 K30 grants were awarded. The last year of funding for these grants is fiscal year 2009. Curriculum development is a core feature of the CTSA program, so 31 of the K30 awards have already merged into the currently funded CTSA sites. For the remaining 20 institutions with K30 awards, most are well positioned to succeed with CTSA applications.

VACCINE SAFETY

Question. Dr. Fauci, given the increased rates of refusal for immunization, the hesitancy of parents who do allow their children to be immunized, and the increased, but fortunately small, outbreaks of vaccine preventable diseases such as measles, please tell us: What resources of the NIH have been allocated to address increasing public concerns about the safety of the U.S. childhood immunization program?

Answer. The NIH has three broad goals in vaccine research: (1) to identify new vaccine candidates to prevent diseases for which no vaccines currently exist; (2) to improve the safety and efficacy of existing vaccines; and (3) to design novel generic vaccine approaches, such as new vectors and adjuvants. To carry out these goals, the NIH supports basic and applied research at 18 Institutes in fields such as immunology, microbiology and disease pathology. Scientific knowledge gained through this basic research provides the foundation to develop new or improved vaccines, treatments, or diagnostics.

NIH does not categorize vaccine safety research funding separately from vaccine research and development funding. Rather, NIH considers vaccine safety to be an integral component of all vaccine research and development. NIH spent just over $1.3 billion on vaccine related research in fiscal year 2007 and estimates $1.3 billion for spending in subsequent years. Federal regulations require that vaccines undergo extensive testing before they can be licensed and distributed. At the NIH, the evaluation of vaccine safety is an essential part of every vaccine clinical trial that we sponsor. Study participants are closely monitored for any adverse effects of the vaccinations they receive. In addition to research on new vaccines, the NIH devotes substantial resources to developing improved vaccines that are more effective and have fewer side effects than currently licensed vaccines. The NIH also pursues research to address specific vaccine safety research hypotheses as they arise. For example, several years ago the NIH supported several studies to find out more about the effects of thimerosal (ethyl mercury) exposure and how it compares with published data on methyl mercury exposure.

Question. Please provide information on resource levels for the past 3 years and for 2009 as proposed, and separate out those funds for smallpox and bioterrorism-related vaccines?

Answer. The NIH has provided the total funding levels for bioterrorism vaccines for fiscal years 2006–2009 in the table below. The NIH does not have funding available for small pox vaccines; however, the NIAID conducts Category A Pathogen Vaccine research which includes the microbes that cause smallpox, anthrax, plague and others. The funding levels for Category A Pathogen Vaccine research for fiscal years 2006–2009 for NIAID only are provided in the table below.

[In millions of dollars]

Disease	Fiscal year			
	2006	2007	2008 (est.)	22009 (est.)
Bioterrorism Vaccines, NIH	481.1	417.2	408.7	415.9
NIAID Category A Pathogen Vaccine Research	258	200	196	200

Question. Also, is there an entity within NIH that looks across Institutes to assure that research is directed at the safety of vaccines? If so, who is responsible for determining priorities in this effort?

Answer. NIH considers vaccine safety to be an integral component of all vaccine research and development, there is no specific entity within NIH that looks across Institutes to assure that research is directed at the safety of vaccines. There are coordinating groups that collaborate on a regular basis to discuss vaccine safety and other related issues in the context of specific diseases or disorders. For example, the NIH Autism Coordinating Committee considers potential underlying mechanisms or triggers for autism-spectrum disorders (ASD), including vaccines. Recently, several NIH institutes developed a Program Announcement (PA) which was released August 2008 to broadly address important scientific questions relating to vaccine safety.

Once in use, vaccines are monitored for safety and efficacy by the Food and Drug Administration (FDA) and Centers for Disease Control and Prevention (CDC). The Federal Government has numerous checks and balances in place to monitor the safety and efficacy of vaccines and to ensure that recommendations about immunization practices and procedures reflect the best available science. It is also important to note the key role of the National Vaccine Program Office (NVPO) within the Department of Health and Human Services, which has responsibility for coordi-

nating and ensuring collaboration among the many Federal agencies involved in vaccine and immunization activities, including NIH, CDC, FDA, and the Department of Defense, among others. Vaccine safety is and will remain a top priority for the NIH.

QUESTIONS SUBMITTED BY SENATOR DANIEL K. INOUYE

WEICKER BUILDING

Question. Dr. Zerhouni, at my request the Congress named the NIH building 36 after the former Senator Lowell P. Weicker. Driving by NIH almost daily, I am reminded that the Lowell P. Weicker building was torn down. I am aware that the building was demolished to facilitate the Master Plan for the Bethesda campus. As the Master Plan is developed, is there a plan to name another NIH building after Senator Weicker?

Answer. Building 36, which bore Senator Weicker's name, has been demolished to make way for a new research building. NIH is currently reviewing the status of existing facilities on our campus, including the naming of buildings. In light of your interest, I will keep you informed as we proceed with our review.

BEHAVIORAL RESEARCH

Question. Dr. Zerhouni, last fiscal year, the committee included report language on the subject of basic behavioral research that stated: "It is therefore requested that the Director submit a report to the committee by December 1, 2007, indicating the scientific leadership structure for this field within the appropriate grant-making Institute." NIH responded in April 2008 with a report titled "Scientific Leadership Structure for Basic Behavioral Research" which reported that 12 of the Institutes fund basic behavioral research totaling approximately $1 billion annually. While many in the field dispute the accuracy of these numbers, the NIH report seems to further strengthen the rationale of the committee's repeated recommendations to NIH that scientific leadership be provided for this important area of research at a grant-making Institute.

While the NIH report of April 2008 provided the committee with a description of the status quo, it failed to address the central question of the need for scientific leadership in the field at the appropriate grant-making Institute. At minimum and as a first step, would NIH agree to create a senior advisory position within NIGMS, which would be filled by a person with appropriate scientific credentials and who would provide leadership and coordination for this important field?

Answer. The NIH created the Office of Behavioral and Social Sciences Research (OBSSR) within the NIH Office of the Director to provide senior advisory leadership and coordination of NIH efforts in these fields. Having a senior advisory position in the Office of the Director allows NIH to fully utilize and coordinate resources across all the Institutes rather than limiting it to one IC. NIGMS is actively supporting basic behavioral research and training. For example, NIGMS has recently hired an individual with a Ph.D. in sociology to help oversee behavioral research and training within NIGMS and coordinate this research with the OBSSR. NIGMS has developed a new predoctoral training program directed toward the interface between basic behavioral and biomedical research and has funded a number of new training grants in this area. Furthermore, NIGMS has taken the lead in supporting social science research on the impact of interventions in developing research careers; specifically, NIGMS has spearheaded two initiatives—one directed to understanding interventions that help underrepresented group participate in research careers and the second (just released) regarding women. See http://grants1.nih.gov/grants/guide/rfa-files/RFA-GM-09-011.html, http://www.nigms.nih.gov/Minority/Interventions.htm and http://www.nih.gov/news/health/jul2008/od-14.htm). Several NIGMS staff members are involved in these programs including the recently hired individual with a Ph.D. in sociology.

Question. The Institute's statutory mandate includes basic behavioral research and training, and the committee has repeatedly stated its belief that NIGMS has a scientific mandate in this area because of the clear relevance of fundamental behavioral factors to a variety of diseases and health conditions. Will the NIH work with the committee to address the need for scientific leadership of this field at NIGMS?

Answer. NIH will work with the committee as these basic behavioral research and training activities continue to develop within NIGMS and across NIH. NIGMS is playing an increasingly important leadership role in supporting basic behavioral research. For example, they have initiated a new predoctoral training program di-

rected toward the basic behavioral-biomedical research interface and are taking the lead in stimulating and supporting research to include key aspects of human behavior in computer models of how infectious diseases spread through populations. They have also taken the lead in supporting social science research directed toward understanding the efficacy of interventions in promoting research careers. They are also continuing their support of behavioral genetics in model organisms.

TRANSLATION OF RESEARCH FINDINGS

Question. Dr. Nabel, you emphasize the importance of the translation of research findings to the clinic and the community. What is NHLBI doing to help communities and physicians adopt interventions that have been shown to be effective, such as the Diabetes Prevention Program, which demonstrated the effectiveness of moderate diet and exercise interventions on preventing development of diabetes?

Answer. The NHLBI translates and disseminates research findings to health professionals, patients, and the public in a number of ways. To ensure that clinicians and patients can avail themselves of the latest scientific knowledge in making health-care decisions, we convene expert panels, which include representatives from other relevant departments and HHS agencies including the CDC, to develop evidence-based clinical guidelines. Updated guidelines for asthma management and control and new guidelines for the diagnosis, evaluation, and management of von Willebrand disease, an inherited bleeding disorder, were released in fiscal year 2007, and the Institute is currently developing the first-ever integrated cardiovascular risk-reduction guidelines for adults and children as well as updating its specific guidelines on adult hypertension, high blood cholesterol, and overweight/obesity.

We also communicate research findings through community education programs. For example, We Can!TM™ promotes maintenance of a healthy weight in children through partnerships and media outreach operating in more than 500 community sites in 46 States, the District of Columbia, and 7 foreign countries. The sites include hospitals, schools, clinics, faith-based organizations, parks and recreation departments, extension services, YMCAs, and State health departments. The Institute also mounts public awareness campaigns such as The Heart Truth for women and heart disease, the leading cause of death among American women, and Learn More, Breathe Better for chronic obstructive pulmonary disease, the fourth most common cause of death in the United States.

The NHLBI supports effectiveness studies to test interventions designed for easy and effective adoption in real-world settings. For instance, in 2006 we funded three clinical trials of strategies to reduce cardiovascular disease risk in obese patients who also have hypertension or metabolic syndrome. Although the primary emphasis is on developing and evaluating weight-loss programs that are effective in routine clinical practice, an important secondary focus is on improving application of evidence-based guidelines to reduce other CVD risk factors.

QUESTIONS SUBMITTED BY SENATOR PATTY MURRAY

NEUROLOGICAL DISEASES

Question. Dr. Zerhouni, neurological diseases, disorders, and injuries affect as many as 100 million Americans—1 out of 3. In addition to the pain that they cause, not just to those suffering but to their families as well, the annual economic burden of neurological illness is over $1 trillion. I will look forward to working with you and your staff to ensure that NIH has the resources it needs to fully explore these important avenues of research. Would you agree that comprehensive, coordinated neurotechnology research should be a top priority for NIH?

Answer. Finding treatments and cures for neurological diseases, disorders, and injuries are high priority for NIH. The NIH budget strongly supports neuroscience research, and programs already underway at NIH ensure a comprehensive, coordinated approach to developing tools and technologies to combat problems that affect the nervous system.

The neuroprosthesis program, which began more than 35 years ago at NINDS, led to the development of cochlear implants, the first practical neuroprosthetic devices, which the FDA first approved in the 1980s and is now used by more than 100,000 people worldwide. Among its many other contributions, this program also made significant contributions to the development of deep brain stimulation (DBS), which the FDA approved for essential tremor and Parkinson's disease in the 1990s, and is continuing to improve DBS technology and expand its application to other diseases. More recently, advanced neuroprosthetics, including those directly controlled

by signals from the brain, are emerging from this research. The NIH neuroprosthesis program, like other NIH neurotechnology programs, coordinates research across several NIH Institutes, including the newest, the National Institute of Biomedical Imaging and Bioengineering.

The Neuroscience Blueprint, begun in 2004, is a cooperative framework among the 16 NIH Institutes, Centers and Offices that support neuroscience research. By pooling resources and expertise, the Blueprint develops tools, training opportunities, and resources to assist neuroscientists in both basic and clinical research. For example, the Blueprint currently supports the development of genetically manipulated mouse models and their use to map gene expression in the brain and to better understand brain development and functioning; neuroimaging studies of normal brain development and neuroinformatics tools to improve brain imaging techniques; and resources and repositories for genetic material as well as neural cell and tissue samples.

Another trans-NIH mechanism, the NIH Common Fund, also supports the development of tools and technologies to benefit all biomedical research, including neuroscience. For example, NIH Roadmap initiatives on bioinformatics and computational biology, on interdisciplinary research, and on "molecular libraries" each support extensive research related to neurological problems.

Finally, I would also like to emphasize that NIH coordinates neurotechnology-related activities with other Federal agencies. The development of neural prosthetics and better treatments for traumatic brain injury are two examples that are particularly important now, because of the injuries to people serving our country in Iraq and Afghanistan. In both these examples, we coordinate extensively not just within NIH but also with the Department of Defense, the Department of Veterans Affairs and other agencies through formal and informal contacts, interagency conferences, review panels, planning meetings, and support of extramural investigators for related projects.

PANCREATIC CANCER

Question. Dr. John Niederhuber, given the fact that pancreatic cancer deaths are increasing, what concrete steps will you take to make this field of study a higher priority?

Answer. NCI continues to fund research to understand the molecular pathways and genomic changes associated with many cancers. Similar genetic changes are seen in several tumor types. For example, Ras is a protein that under normal conditions regulates cell growth. When mutated it can cause uncontrollable cell growth or cancer to occur. Ras is associated with prostate, breast, colon, and pancreatic cancer among others. Further understanding Ras will help identify targets for new drugs and therapies for pancreatic cancer.

In addition, NCI will continue to invest specifically in pancreatic cancer research. For example, NCI's major new initiatives—including the NCI Alliance for Nanotechnology in Cancer and the Cancer Biomedical Informatics Grid (caBIG)—hold a great deal of promise for improving and extending the lives of pancreatic cancer patients.

These efforts have resulted in a strong infrastructure and cutting-edge scientific research program to study all aspects of pancreatic cancer including prevention, early diagnosis, and therapy. It is expected that NCI's support of pancreatic cancer research and resulting science advances will continue to increase.

Question. We've seen how important early detection tests have been in reducing mortality for other cancers. How far away are we from finding an early detection test for pancreatic cancer?

Answer. While it is very difficult to estimate how far we are from a new diagnostic test, the peer-reviewed NCI-supported projects listed below are part of multiple NCI activities that are relevant to reaching that goal.

—Commonly used imaging methods, such as endoscopic ultrasound, abdominal CT scan, or MRI, are inadequate for the detection of early stage pancreatic cancer. This has led to NCI's investment in a portfolio that includes multiple relevant early biomarker detection research projects. Sixteen early detection biomarkers for pancreatic cancer are in pre-validation studies with others rapidly being added to the validation pipeline.

—CA 19—9 is presently the most widely used serum marker for pancreatic cancer, but as a screening test in an asymptomatic population, its positive predictive value is below 1 percent. Early Detection Research Network (EDRN) investigators are actively exploring both genomic and proteomic markers to improve the ability to detect early stage pancreatic cancers.

—Scientists at the University of Texas M.D. Anderson Cancer Center are also taking a targeted approach to identify biomarkers for early detection of pancreatic

cancer by focusing on abnormal genetic pathways. They have identified a number of genes that are consistently differentially expressed in pancreatic cancer and are examining these genes as candidate biomarkers.

Question. How much funding would you need to find a pancreatic cancer early detection test?

Answer. NCI will continue to make progress in the understanding pancreatic cancer and finding ways to diagnosis the disease early. The development of advanced technologies, new research projects, and a cadre of expert scientists working on the problem are critical to this effort. As noted above, NCI is supporting a number of early detection research initiatives and promising results have been realized. While it is impossible to say how much funding is needed to develop an early detection test for pancreatic cancer, investment in cancer research has never been more critical or more needed.

Question. How is the NCI prioritizing this effort given that pancreatic cancer is one of the deadliest forms of cancer and is currently the fourth leading cancer killer?

Answer. NCI recognizes the importance of pancreatic cancer research efforts. For example, a pancreas state-of-the-science meeting was held at NCI in December of 2007 to bring together investigators and other stakeholders to develop a research agenda for adenocarcinoma of the pancreas over the next 3–5 years. Based on input from the meeting, the Gastrointestinal Scientific Steering Committee of the NCI Clinical Trials Working Group (CTWG), working with cooperative groups and other groups that are active in pancreatic cancer clinical research, are developing strategic priorities for future clinical trials. Their recommendations will be disseminated to the relevant oncology, imaging and translational research communities.

In addition, the Pancreatic Cancer Research Map (http://www.cancermap.org/pancreatic/index.jsp) was recently developed as a tool for tracking pancreatic cancer research, clinical trials, and investigators. The map is a collaborative project between NCI, the Pancreatic Cancer Action Network (PanCAN), and the Lustgarten Foundation for Pancreatic Cancer Research. The map is designed to facilitate and expedite collaborations among researchers in the pancreatic cancer research community by helping them find related projects in pancreatic cancer research and network with other researchers, and also to identify funding opportunities specific to pancreatic cancer research.

As mentioned above, NCI is also supporting major new initiatives—including the NCI Alliance for Nanotechnology in Cancer, PanScan, and the Cancer Biomedical Informatics Grid (caBIG)—which have great potential for advancing pancreatic research.

QUESTIONS SUBMITTED BY SENATOR ARLEN SPECTER

NIH FUNDING

Question. Dr. Zerhouni, on May 23, 2008, I wrote to you asking "how much would it cost to cure cancer or at least make a major frontal attack on the many strains of cancer?" You responded with an estimate of $5.2 billion ($1.2 billion for NCI and $4 billion for the rest of NIH). Could you please elaborate on the need for this funding with respect to finding cures for cancer and other diseases?

Answer. Despite the extraordinary progress made across all fields of biomedical sciences funded by the NIH in the past 50 years, we still do not know much of the basic biology that is needed to cure the more than 200 types and subtypes of cancers our patients battle daily. Much more work is needed to speed progress.

As the NIH Director, I have witnessed a great acceleration in the pace of discoveries, many derived from the completion of the Human Genome Project in 2003. These discoveries provide unprecedented research opportunities across all disease areas. The National Cancer Institute (NCI) and the National Human Genome Research Institute (NHGRI) are currently collaborating in a Cancer Genome initiative. In July 2008, a pilot study by NCI and NHGRI produced new clues of genetic factors that play an important role in one of the most aggressive forms of brain cancer. Similarly, a landmark study identified new genes, and therefore, new leads in understanding autism, a disease of growing and grave concern to all of us. These are examples of the almost weekly reports I received of the discovery of novel factors in many diseases, as opposed to a few reports per year at the beginning of my tenure in 2002.

Given the nature of scientific discovery, any estimates about exact costs and timing of breakthroughs in any disease are uncertain. Moreover, we have seen progress in one disease often comes from unrelated areas of investigation, thus, we must support a wide range of approaches across all fields of science.

Question. Why do you feel that the success rate for grant proposals should be 30 percent instead of the 18 percent currently projected?

Answer. The success rate of 30 percent for grant proposals would contribute to scientific progress. We estimate the success rate of research applications could be 18 percent in fiscal year 2009. Young investigators too often become discouraged and opt for other careers, depleting the ranks of the next general of scientists and depriving the Nation of important new talent and ideas that could exploit the unprecedented opportunities NIH research has made possible and help keep our Nation competitive in this strategic area.

Question. For all witnesses: Senator Harkin and I have introduced legislation providing an additional $5.2 billion to the NIH. What activities would you emphasize with additional funds?

Answer. Efforts to prevent, detect, and treat disease require better understanding of the dynamic complexity of the many biological systems of the human body and their interactions with our environment at several scales—from atoms, molecules, cells and organs, to body and mind. As the questions become more complex, and even as knowledge grows, research itself becomes more multi-faceted. With additional resources above the $29.5 billion requested in the President's budget for NIH as proposed in your legislation, much work could be done to speed progress.

These funds would allow NIH to leverage scientific opportunities in areas like:

—*Research Pipeline*.—Additional funds will provide NIH with the ability to increase its focus on the troubling trends in training and research career support, which will affect the pipeline of researchers for many years in the future. Examples include: Training programs for pediatric diabetes researchers; increased career development awards; increased trainees; opportunities to train new clinical researchers; more support for Malaria research training programs; increased training in informatics; and expanded women's health training programs.

—*Repositories*.—Additional funds would allow NIH the ability to expand critical data and tissue repositories. Examples include: expand tissue repositories for breast and prostate cancer; expanded Human Genetics Repository; expanded support for in-depth analysis of data collected from whole genome association studies; support for research related to the Genome-wide Association Studies (GWAS) findings; and increased applications/utilization of GWAS data.

—*Clinical Trials*.—Additional funds would provide NIH the ability to expand in the area of clinical trials research. Examples include: expand the special program of translational research in Acute Stroke centers; launch a study to treat children with critical asthma; fund more studies in certain minority populations, including Asian Americans and Native Americans; support an initiative in Noise-Induced Hearing Loss; increased support for the Bipolar Trials Network; and increased support for Phase III trials in medications development.

—*Technologies*.—Additional funds would provide NIH the ability to pursue next-generation technologies that will facilitate research progress. Examples include: work to increase non-invasive functional monitoring to improve clinical studies in kidney diseases; increase investment in projects related to the Brain-Computer Interface; ensure steady program in research to develop the $1,000 genome; and increase NIH's ability to pursue opportunities in advanced imaging and delivery technologies.

In addition to the examples provided above, NIH could support nearly 1-in-3 of every application received, for a success rate of 30 percent.

Question. Have the flat funding levels provided to the NIH over the past 5 years seriously harmed the United States research enterprise?

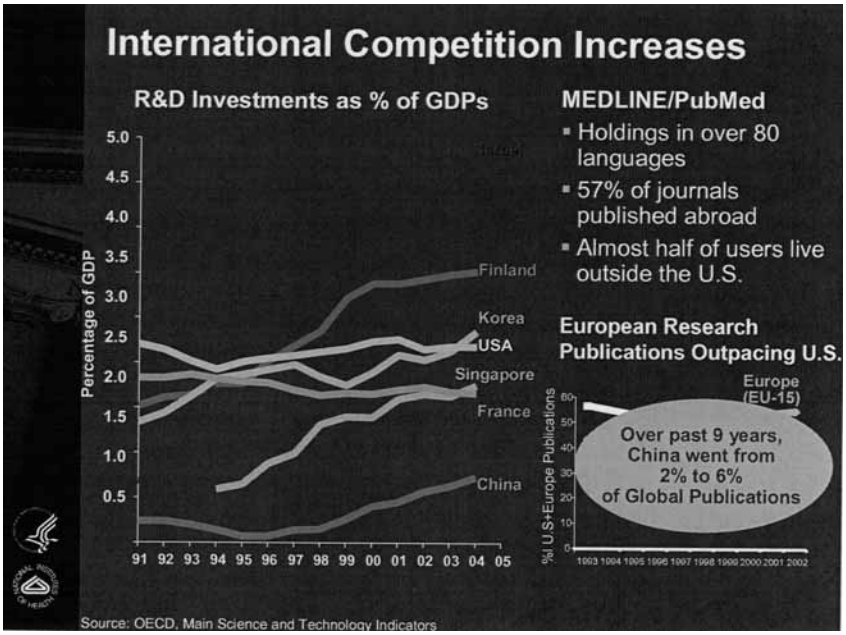
Answer. Within resources available, currently $29.5 billion in fiscal year 2008, NIH has supported the highest priority research. Recent budgets have reduced overall purchasing power for the biomedical research community and have required NIH to make tough decisions on how resources are allocated. The success rate for applicants receiving awards has declined from 30 percent in fiscal 2003 to 21 percent in fiscal year 2007 and an estimated 18 percent in fiscal year 2009, though the rapid rise in the number of applications submitted has also been a major factor.

Some of the ways in which NIH has managed current resources across the Institutes and Centers include: reducing/delaying support for clinical trials; scaling back certain research training programs; data and tissue repositories have not been expanded as initially planned or have been deferred; and slowing or deferring the planning for developing specific computer interface, non-invasive monitoring, and advanced imaging and delivery technologies.

The fiscal year 2009 request will, however, continue to move science forward. We will continue to invest in the best science and work with the community to use the resources provided to develop and translate scientific advances into therapies, cures, and diagnostics.

Question. Is our international scientific pre-eminence in jeopardy due to these flat budgets?

Answer. The United States is now the pre-eminent force in biomedical research. Our Nation continues to lead the highly competitive biotechnology and pharmaceutical sectors. Yet, we are also the focus of increasing competition from growing research in Europe and Asia. We must continually sustain the momentum of U.S. biomedical research. The table below reflects the increased rate of global competition.



STEM CELLS

Question. Dr. Zerhouni, you have publicly stated that it is time for scientists to have access to more embryonic stem cell lines. Under your leadership, NIH funding for stem cell research has slowly but steadily grown and the work of the NIH stem cell unit to characterize the available stem cell lines has been excellent. When the ban on funding for additional lines is rescinded, how would you suggest the NIH work to realize the full potential of embryonic stem cells as quickly and efficiently as possible?

Answer. NIH keeps abreast of the current policies that guide Federal funding of human embryonic stem cell (hESC) research. We will modify these policies and the eligibility criteria for Federal funding, including the rapid development of Guidelines, as necessary, taking into consideration all the information currently available. In addition, NIH continues to rapidly assess research needs and opportunities in stem cell biology and develop initiatives that meet those needs to capitalize on these opportunities, consistent with existing policies.

Question. Dr. Nabel, a recent report in the journal Nature described how a laboratory was able to turn human embryonic stem cells into heart progenitor cells and sort them from the non-heart cells. Please explain why this advance is important and how stem cells may one day be used to treat heart disease or test prospective heart drugs.

Answer. The investigators reporting in the journal Nature successfully used human embryonic stem cells to produce cardiovascular progenitor cells that, in turn, were able to differentiate into the three cell types needed to form the human heart—cardiomyocytes (to make the heart muscle), smooth muscle cells, and endothelial cells (to make blood vessels). This is an important step toward development of new strategies to regenerate damaged hearts.

Heart progenitor cells have great potential for the repair of heart muscle injured by myocardial infarction or other cardiac diseases. Researchers hope that injection

of the cells into patients early after a heart attack, either through the coronary arteries or directly into the muscle, could help to restore heart function and prevent the development of heart failure. In patients with chronic heart disease who have already developed heart failure, the cardiac progenitor cells may be able to restore the heart's ability to pump effectively.

LP(A)

Question. Dr. Nabel, is there anything new that you can tell me about the status of research toward a medication that lowers LPa?

Answer. There is little evidence that lowering Lipoprotein (a) (Lp(a)) with specific drugs reduces cardiovascular risk. In fact, based on the current scientific evidence, Lp(a) measurement is not recommended as a screening tool for cardiovascular disease (CVD) risk in the general population, but only for individuals with a personal or family history of early-onset heart disease. At present, if an individual is found to have elevated levels of Lp(a), the recommended treatment strategy, which is supported by clinical trial evidence, is to aggressively lower the individual's LDL cholesterol with statins to decrease overall CVD risk.

The Institute will continue to review the scientific evidence related to emerging CVD risk factors such as Lp(a). We are currently in the process of updating the Adult Treatment Panel (ATP) guidelines of the National Cholesterol Education Program, an evidence-based set of guidelines on cholesterol management published in 2001. As part of that effort, the expert panel developing ATP IV will evaluate the evidence that Lp(a) confers risk for CVD and will consider the evidence regarding whether Lp(a) lowering is warranted.

HIV/AIDS VACCINE

Question. Dr. Fauci, you recently called for a re-evaluation of our efforts toward finding an HIV/AIDS vaccine. Why have we had so many false starts toward HIV/AIDS vaccines and how should we approach the problem in the future?

Answer. There is rarely a clear pathway to developing a vaccine, and it is not unusual for investigational vaccines to fail. It took decades to develop currently licensed vaccines to combat typhoid, pertussis, polio, and measles. Science is iterative, and from each product that fails in clinical trials, we learn something that informs the next clinical trial.

HIV vaccine development has been challenging for a number of reasons, including the fact that the virus mutates rapidly, hides from the immune system, and targets and destroys the immune system cells that are successful in fighting and clearing most other viruses from the body. With HIV we will have to do better than nature if we are to develop a vaccine, unlike the situation with other viral diseases such as measles and influenza, where we have succeeded in inducing protective responses with vaccines by mimicking the response to natural infection. And because of safety concerns, vaccine approaches commonly used to fight other infectious diseases, such as the live attenuated (weakened) or killed viruses used in other vaccines, are not tenable in HIV vaccine development.

The failure of the Merck HIV vaccine candidate used in the STEP clinical trial prompted NIAID to re-evaluate our HIV vaccine research efforts. We initiated numerous consultative meetings with scientific experts and various stakeholders on how best to reinvigorate and advance HIV vaccine research in the wake of the STEP trial, culminating in an HIV vaccine summit on March 25, 2008. Those discussions revealed widespread consensus that the development of a safe and effective HIV vaccine will require significant advances in our understanding of the virus and an increased emphasis on basic vaccine discovery research to learn more about immune responses and better identify potential vaccine candidates while simultaneously advancing the most promising vaccine candidates into human clinical trials when appropriate.

NIAID has already taken a number of steps designed to achieve a more appropriate balance between vaccine discovery and clinical development. In May 2008, we supported a new program to study the response of B-cells to HIV infection—a departure from previous efforts, which had focused on T-cell response. NIAID also began two new major initiatives designed to support investigator-initiated grants for discovery research on HIV vaccines and tactics to interrupt HIV transmission. We are also expanding non-human primate research to support HIV vaccine discovery, and improved animal models are being developed for use in the pre-clinical evaluation of vaccine candidates and to identify correlates of immunity. Lastly, NIAID created a Vaccine Discovery Branch in the Vaccine Research Program within the Division of AIDS to help build bridges between basic researchers and HIV vaccine designers,

identify gaps in knowledge needed to develop an HIV vaccine, and promote research to fill those gaps.

GENETICS RESEARCH

Question. Dr. Collins, the Human Genome Project was completed in 2003. What is left to do in the area of genetics research?

Answer. After leading the Human Genome Project to the successful completion of its extraordinary goal of sequencing the entire human genome in 2003, NHGRI expanded its mission to encompass a broad range of studies aimed at understanding the structure and function of the human genome and its role in health and disease. To that end, NHGRI supports the development of resources and technology that will accelerate genomic research and its application to human health, thus enabling truly pre-emptive, predictive, personalized, and participatory health care.

Question. What practical medical benefits have been achieved and what will soon be available?

Answer. The Human Genome Project has led to important discoveries related to genetic predisposition to some of the most common causes of morbidity and mortality in the United States today. These discoveries can lead to improved diagnostic, therapeutic, and pre-emptive approaches. Examples are listed below.

—*Type 2 Diabetes*.—Nearly 20 new genetic markers have been discovered to be associated with type 2 diabetes. For example, homozygosity—that is, having two identical forms of a gene—or TCF7L2 gene mutations has been shown to convey a 140 percent increased risk of type 2 diabetes.

—*Heart Disease*.—Multiple new markers associated with coronary heart disease have been discovered. For example, homozygosity for a variant on chromosome 9p21—as occurs in approximately 25 percent of people of European ancestry—increases risk for coronary artery disease by an estimated 60 percent.

—*Breast Cancer*.—A number of genetic markers are now known to affect risk for developing breast cancer. Recently-discovered variations in the FGFR2 and CASP8 genes are associated with a 13–26 percent increase in risk of developing breast cancer.

—*Prostate Cancer*.—Variations in several genes on chromosome 8 have been shown to be associated with 30–50 percent increase in the risk of prostate cancer.

—*Age-Related Macular Degeneration (AMD)*.—Five genes have been found to account for over 70 percent of the incidence of age-related macular degeneration, which is the leading cause of severe vision loss in older Americans. Each of these genes is associated with a 30–160 percent increased risk of AMD.

The Human Genome Project has led to improved diagnostic testing, with diagnostics now available for more than 1,300 genetic disorders, and also to improved prognostic testing, such as microarray-based assays like MammaPrint and Oncotype DX that predict breast cancer recurrence and guide treatment options.

The HGP has also led to the rapid development of pharmacogenomics, giving physicians the ability to prescribe a wide range of medications more safely. For example, a recent study has shown that HLA—B*5701 testing effectively predicts potentially severe adverse reactions to the HIV medicine abacavir.

Susceptibility to disease is only part of the picture. The HGP has also enabled development of many new drugs targeted at diseases such as age-related macular degeneration, myocardial infarction, and melanoma. In addition, the NIH Roadmap project on Molecular Libraries enables direct translation from gene discovery to treatment by finding new uses for pre-existing drugs and identifying small molecule, drug-like compounds that can serve as starting points for new treatments. For example, this approach was recently used by the NIH Chemical Genomics Center (NCGC) to identify a potential new treatment against the parasitic disease, schistosomiasis, which affects upwards of 200 million people in the developing world, causing an estimated 280,000 deaths annually.

CANCER

Question. Dr. Niederhuber, what is your projection on when cancer—or many cancers—will be treatable or curable? Also, in a response to a question from me, the cancer community has indicated that $335 billion over the next 15 years is necessary to make real progress toward cancer cures. What do you think is necessary in terms of time, funding, and research breakthroughs to make a real difference in curing cancer?

Answer. Cancer, as you know, is not just one disease. It is perhaps as many as 1,000 different diseases, and as such it is a very complex and dynamic process. Unfortunately, I can't give you a timeframe for how long it will take to cure cancer

or make it much more than a chronic set of diseases that we can prevent or live with. However, we're learning and understanding more and more every day, and we are gaining vital new knowledge that will get us closer to our goal.

As the leader of the National Cancer Program, NCI is, today, building on its history of research success and wisely spending every dollar it receives, in a continual effort to foster the best research and to connect the public, private, and academic sectors for effective translation of these discoveries. If NCI were to receive the increase of $1.2 billion identified in the fiscal year 2009 by-pass budget, then NCI could better lead these collaborations and connectivity—to shorten the path from an innovative discovery in the laboratory to making an effective difference with a patient in the clinic. Listed below are some potential investments:

—Increase the number of new investigators;
—Expand research training opportunities;
—Rebuild scientific infrastructure;
—Expand caBIG;
—Raise RPG success rate and average cost per grant;
—Expand Cancer Centers program;
—Invest in intramural program;
—Expand The Cancer Genome Atlas;
—Increase Drug Development;
—Re-engineer Clinical Trials;
—Fund early phase pharmacodynamic studies;
—Create a U.S. oncology tissue bank;
—Establish certified centralized tumor characterization labs;
—Enhance technological efforts around nanoparticles and proteins
—Enhance technology development in clinical proteomics;
—Invest in systems biology;
—Increase biomedical computing capabilities; and
—Develop imaging tools.

To effectively operationalize this plan would require that we build scientific capacity. We must maximize our efforts to recruit and sustain the very best and brightest to work on cancer. As in the past, an investment in understanding the complex systems involved in cancer initiation and growth will continue to impact our understanding and treatment of all diseases—acute and chronic.

CONCLUSION OF HEARINGS

Senator HARKIN. So, thank you all very much, that concludes our hearings.

[Whereupon, at 11:56 a.m., the hearings were concluded, to reconvenue subject to the call of the Chair.]